American Journal of Diseases of Children

VOLUME 61 MAY 1941 NUMBER 5

COPYRIGHT, 1941, BY THE AMERICAN MEDICAL ASSOCIATION

EVOLUTION OF HEMIPLEGIAS IN INFANCY

RANDOLPH K. BYERS, M.D.

BOSTON

Hemiplegia of infancy has usually been noted first at the time the child began to walk, and it has generally been stated by parents and physicians that they had noted nothing wrong with the baby prior to this time. On the other hand, in the vast majority of instances there has been nothing in the recent past history of the infants to suggest that damage to the nervous system had occurred just prior to the first observation of the hemiplegia. In a large clinic devoted to the care of patients with motor disturbances other than poliomyelitis, there have appeared recurrently children with hemiplegia on whom a diagnosis of brachial palsy had been made. This mistake has been so constant as to suggest a real medical misapprehension; the diagnosis of brachial palsy had been made in the first half of infancy, only to have the cerebral nature of the disorder become manifest later in infancy.

Recent publications by Kennard [1] have called my attention to the importance and significance of the error. She studied a group of infant monkeys and chimpanzees who had been experimentally deprived of varying amounts of cerebral cortex early in infancy. She found that the early removal of motor and premotor cortex from infant monkeys produced no definite motor abnormalities immediately but that as the animals developed the primitive grasp reflex remained longer in the hand innervated from the removed cortex than in its healthy fellow and that as fine finger movements began to develop clumsiness of the affected hand became apparent. Save for these minor disturbances, however, no

A grant from the Commonwealth Fund made possible the work here reported.

An abstract of this paper, with discussion, was published in a previous number of the AMERICAN JOURNAL OF DISEASES OF CHILDREN (**60**:446 [Aug.] 1940) in the transactions of the annual meeting of the American Pediatric Society, Skytop, Pa., May 2, 1940.

1. Kennard, M. A.: (*a*) Age and Other Factors in Motor Recovery from Precentral Lesions in Monkeys, Am. J. Physiol. **115**:138-146, 1936; (*b*) Recovery of Function in Infant Monkeys Following Cortical Ablations, ibid. **123**:118, 1938; (*c*) Reorganization of Motor Function in the Cerebral Cortex of Monkeys Deprived of Motor and Premotor Areas in Infancy, J. Neurophysiol. **1**:477-496, 1938; (*d*) The Relation of Age to Motor Impairment in Man and Subhuman Primates, Arch. Neurol. & Psychiat. **44**:377-397 (Aug.) 1940.

motor signs or symptoms resulted. When the operation was performed early in infancy, more extensive ablations were necessary to produce hemiplegia. The earliest abnormality following such operations was paresis, which was more marked in the contralateral arm and leg and most marked in the distal portions of the arm. Only as the animals became more mature (the hemidecorticate monkeys were 2 years old) did increased resistance to passive movement and increased tendon reflexes appear.

Removal of the motor and premotor cortex from a 4 month old chimpanzee produced paresis, which was evident as decreased activity in the contralateral extremities; but increased tendon reflexes were not demonstrable before the sixth month, and not until the eighth month did increased resistance to passive movement appear. As a result of her experiments Kennard [1d] concluded:

> The two factors in (cortical) motor deficit, namely paresis and spasticity, are more clearly distiguishable in the infant than in the adult. With development of the animal operated on in infancy, paresis appears first and is a negative quality, a failure of the abnormal extremities to develop fine coordinate movements; much later, spasticity appears, as a positive element, an added resistance to passive manipulation.

For a further discussion of the subject and a bibliography Kennard's articles should be consulted.

Two other articles pertinent to the present discussion may be briefly considered. From the physiologic point of view the report of Langworthy [2] on the results of decerebration of immature animals is of interest. He reported that if rabbits or opossums, which are born in an immature state after a brief gestation period, are decerebrated at birth decerebrate rigidity does not occur; instead, the animals remain hypotonic and subject to extremely persistent and active running movements as the result of slight stimuli. If, on the other hand, newborn guinea pigs, which are born in a relatively mature state after a long gestation period, are decerebrated, typical decerebrate rigidity appears. Kittens, which at birth are more mature than rabbits and less mature than guinea pigs, occupy an intermediate position in respect to the degree of decerebrate rigidity. Without entering into a discussion as to the identity of decerebrate rigidity and hemiplegic spasticity, one may say that these observations demonstrate at least that different results are obtained when the brain is mutilated prior to the development of adult postural patterns than when the same mutilating procedures are carried out after the establishment of such patterns. Langworthy related these differences to the maturation of the rubrospinal tracts in the animals used.

---

2. Langworthy, O. R.: Relation of Onset of Decerebrate Rigidity to the Time of Myelinization of Tracts in the Brain Stem and Spinal Cord, Contrib. Embryol. (no. 89) **17**:125, 1926.

From the pathologic point of view McNutt [3] reported the results of autopsies on 2 infants, 1 of whom died at 6 days and the other at 22 days of age. During life they exhibited weakness and paralysis of an arm, followed by convulsive twitchings and finally by evidences of increased intracranial pressure. At autopsy large hemorrhages were found overlying the cortex on the side opposite the affected arm, and in the older patient the hemorrhage had caused so much atrophy of the cortex in the rolandic area that the mass of blood had nearly reached the lateral ventricle.

Besides hemorrhages in the subdural or subarachnoid spaces, other mechanisms capable of injuring the cortex have been described. Schwartz and Fink [4] dealt with what they called the "suction effect" of the relatively reduced pressure over the presenting part after the fetal membranes had ruptured during labor. They showed that edema and hemorrhage may occur in the skull and the brain tissue beneath the caput succedaneum of the newborn child. Their report has never been accorded the general recognition it merits. Anoxemia due either to deprivation of oxygen or to loss of blood could probably produce the same result, and injuries from diseases and developmental defects have, of course, been reported.

Flaccid hemiplegia acquired late in life has been well known for some time. Aring [5] recently discussed the disorder and reported a series of cases with autopsy. In every instance the hemiplegia remained flaccid over long periods and did not tend to improve. At autopsy, the deep structures of the hemisphere were always involved. It will be obvious that the clinical course of the infants to be described in the present report varies radically from that of Aring's patients.

MATERIAL

In order to study the subject further the records of the Muscle Training Clinic of the Children's Hospital, Boston, were reviewed. Seven cases were readily found in which a physician had made a diagnosis of brachial palsy early in infancy only to have cerebral spastic hemiplegia appear later. Seven additional cases were encountered in which a good description of early flaccid paresis was given by the mother or by the district nurse, who had referred the patient to the hospital because it was thought that the infant probably had brachial palsy. Finally, because surgical procedures demonstrated the presence of cerebral pathologic changes, the case of an infant which was seen in consultation because of "brachial palsy" on the seventh day of life has been included.

3. McNutt, S. J.: Apoplexia Neonatorum, Am. J. Obst. **18**:73-81, 1885.

4. Schwartz, P., and Fink, L.: Morphology and Genesis of Hemorrhages in Brain and Skull of the Newborn Due to Labor, Ztschr. f. Kinderh. **40**:427, 1925.

5. Aring, C. D.: Flaccid Hemiplegia in Man, Arch. Neurol. & Psychiat. **43**: 302-317 (Feb.) 1940.

Data on Fifteen Infants with Hemiplegia

Case Number	Natal and Neonatal Circumstances	Age When Motor Defect First Noted; By Whom	Character of Early Motor Defect	Age at Subsequent Examination	Character of Subsequent Motor Defect	Pathologic Evidence	Age When Pathologic Data Were Obtained
1	Mother ill with influenza at delivery; patient in bad condition for 2 weeks	3 mo.; local physician	Right arm weak; "brachial" palsy	1½ yr.	Spastic hemiplegic gait	Encephalogram showed marked atrophy of left cerebral hemisphere, with shift of the ventricular system to the left and enlargement of the left ventricle	15 yr.
		6 mo.; mother	Right arm and leg weak	11 yr.	Total hemiplegia, including face; increased resistance to passive movement of both left extremities; increased tendon reflexes on left; Babinski sign on left		
2	Low forceps delivery at full term; birth weight 9 lb. 10 oz. (4,366 Gm.); hematoma over left eye and right occipital region	3 days; mother	Left arm weak	17 mo.	Left hemiplegia; marked increase in resistance to passive movement of both left extremities; increased tendon reflexes	Bloody spinal fluid; no subdural hematomas on burr hole examination	15 days
		12 days; hospital staff	Left arm motionless and without tendon reflexes; other reflexes normal; convulsions, including left arm				
3	Forceps delivery; difficulty in initiating respiration	At birth; local physician	Left arm limp and not used	5 yr.	Left hemiplegia, including face; marked resistance to passive movement; atrophy of left side, including face; lively tendon reflexes	.....	....
		6 wk.; hospital staff	All movements present but weak; "Horner's syndrome on left"; tendency to contracture of internal rotator muscles of shoulders; "brachial palsy"				
4	Breech delivery at term; difficulty in initiating respiration; patient would not suck and swallowed poorly for 4 or 5 days	8 mo.; mother	Right arm weak and not used as well as left; patient did not sit up; "brachial palsy"	10 mo.	Tonic neck reflexes; hyperactive knee jerks; right arm floppy but with increased resistance to passive movement; patient just beginning to stand alone at 4 years of age	.....	....
		9 mo.; hospital staff					

5	High forceps delivery at term	3 mo.; hospital staff	Right arm showed generalized weakness; tendon reflexes normal; "brachial palsy"	1 yr.	Right hemiplegia; increased tendon reflexes on right; increased resistance to passive movement	.....	....
6	Normal delivery at term; hemorrhagic disease second day of life; no details	2-3 mo.; mother 4 mo.; hospital staff	Right arm and hand showed generalized weakness and flaccidity; grip weak; patient was unable to elevate arm above shoulder	18 mo.	Right hemiplegic gait; contractures; increased tendon reflexes on right; increased resistance to passive movement on right; atrophy of right extremities; clonus and Babinski sign on right	.....	....
7	Normal delivery; almost died on second day as result of profuse umbilical hemorrhage	3 mo.; district nurse 4 mo.; hospital staff	Right arm weak and flaccid Right arm limper than left and not used as much; tendon reflexes present and normal in all extremities; tendency to cross legs	6 mo.	Obvious right hemiplegia; increased tendon reflexes on right; Babinski sign on right	.....	....
8	Forceps delivery at term; no neonatal difficulty	24 hr.; mother 2 wk.; hospital staff	Left arm weak and motionless Left arm flaccid, especially at shoulder and elbow	1 yr.	Left hemiplegia, including face; increased resistance to passive movement on left; patient too uncooperative for examination of reflexes	.....	....
9	Normal delivery at term; no neonatal symptoms	3 days; mother	Right arm and hand weak and motionless; at 1 year of age right leg was "used wrong"	1½ yr.	Right hemiplegia, including face; increased resistance to passive movement; Babinski sign on right; increased tone in flexor muscles of right arm and extensor muscles of leg; forced grasping; right tendon reflexes increased	.....	....
10	Normal.....	12 mo.; hospital staff	Weakness on right side of four days' duration; right arm not used voluntarily; right side of face and right leg not moved as much as left; musculature hypotonic; grasp reflex on left; acute syphilitic meningitis; "poliomyelitis" was diagnosis on admission	3 yr.	Right hemiplegia; contracture of right tendo achillis; increased tendon refleves on right	Acute syphilitic meningitis	....

Data on Fifteen Infants with Hemiplegia—Continued

Case Number	Natal and Neonatal Circumstances	Age When Motor Defect First Noted; By Whom	Character of Early Motor Defect	Age at Subsequent Examination	Character of Subsequent Motor Defect	Pathologic Evidence	Age When Pathologic Data Were Obtained
11	Birth and neonatal period normal	4-5 mo.; mother 5 mo.; local physician	Right arm weak and not used to grasp toys "Brachial palsy"	4½ yr.	Right arm weak, especially in movements of fingers and hand; increased resistance to passive movement of right leg; tendon reflexes in arm and leg increased; Babinski sign on right	.....	....
12	Normal delivery under ether anesthesia; no neonatal symptoms	3 mo.; mother	Right arm and leg weak and not used as much as left	22 mo.	Right hemiplegic gait; tendon reflexes on right increased; hand clumsy and stiff; forced grasping; Babinski sign on right; contracture of right tendo achillis	.....	....
13	Normal delivery at full term; hemorrhagic disease second day of life; no cerebral symptoms	2 wk.; mother 5 mo.; local physician	Left arm blue and weak Left arm weak; patient referred to hospital and accepted as having "brachial palsy"	2½ yr.	Left hemiplegia; atrophy of left side of face and both lower extremities; left arm hypotonic, with increased reflexes and marked weakness; left leg showed increased resistance to passive movement and increased reflexes	.....	....
14	Normal delivery at full term; no neonatal difficulties	3 mo.; mother 10 mo.; hospital staff	Left arm weak; left leg not moved as much as right at 6 months of age; "brachial palsy"	14 mo.	Left hemiplegia, involving face; left arm hypotonic, with increased reflexes; left leg showed marked increase of resistance to passive motion and increased reflexes; contracture of left tendo achillis	.....	....
15	Difficult forceps delivery; left clavicle broken; mother had pneumonia	At birth; local physician	Right arm weak and motionless; right leg moved less than left; total scoliosis, convexity to right; convulsions on left side; no tendon reflexes in left arm	.....	.....	Left subdural hematoma with organizing membrane; subdural fluid from right side clear; no membrane	14 days

ETIOLOGIC FACTORS

It is evident from the table that the series of patients includes a high proportion of babies whose births or neonatal periods were abnormal. In two instances the mother was acutely ill at the time of delivery, and the infant was considered to be in poor condition. Five of the babies were delivered by forceps, and in 1 of these, who showed a right occipital hematoma, left hemiplegia later developed. One infant was delivered by breech extraction, another nearly died of exsanguination when his umbilical cord became untied on the second day of life and 2 had hemorrhagic disease of the newborn, which required transfusion. Thus, 10 of

Fig. 1 (case 1).—Encephalogram made at 15 years of age, showing marked enlargement of the left ventricle and shift of the ventricular system toward the left.

the 15 infants had much more than the usual chance of suffering injury to the cortex during birth or the neonatal period.

In 1 of the 5 remaining patients flaccid hemiplegia developed at the age of 1 year, in the course of syphilitic meningitis, but for the disorders of the other 4 no etiologic factors were discovered.

PATHOLOGIC AND LABORATORY EVIDENCE

Since none of the infants died no autopsy data are available, but a few scattered anatomic data exist. Convulsions developed in the patient in case 1 at 15 years of age, and an encephalogram showed marked enlargement of the lateral ventricle opposite the spastic limbs, with

marked shift of the entire ventricular system toward the enlarged ventricle. Crothers [6] showed that enlargement of a lateral ventricle and marked shift of the entire ventricular system toward it take place only when the injury occurs early in infancy or during fetal life, and then only if the spared hemisphere remains substantially intact. He expressed the belief that growth of the healthy hemisphere produces the displacement. Consequently, the distortion of the ventricles in the present case is regarded as evidence that the cerebral damage occurred early in infancy.

From the right subdural space of the last patient, seen in consultation because of "right brachial palsy" and twitching of the face on the opposite side, 10 cc. of free, blood-tinged serous fluid was removed by needle puncture, and from the left subdural space 2 or 3 cc. of blood-tinged fluid was removed. Burr holes showed no organizing membrane on the right, but an encapsulated collection of blood-tinged fluid on the left was removed by Dr. Franc Ingraham. After the removal of the subdural hematoma there was a rapid increase in the movement and tone of the paretic right arm and leg. In the second patient, who had a practically identical course and grossly bloody spinal fluid, burr hole exploration revealed nothing abnormal.

As has already been indicated, the tenth patient had meningitis accompanied by a great increase in the pressure and lymphocyte count of the spinal fluid and positive Wassermann reactions of the blood and spinal fluid.

CLINICAL COURSE

In all cases the first symptom noted was weakness of an arm, but in only 2 cases of the 14 in which the condition either was presumed to be congenital or originated in the neonatal period was the weakness noted at birth. In the remaining cases weakness was observed for the first time at intervals varying from twenty-four hours to eight months after birth.

In most instances the paretic arm was simply described as "weak" or "not used as much as the normal one"; the word "motionless" was used either by the parents or by the physician in only 3 cases. In many instances no note was made about the presence or absence of tendon reflexes, which, unless they are active, are difficult to elicit in small infants. In 4 instances the tendon reflexes in the paretic arm were mentioned, twice as absent and twice as normal. The range of passive movement at the wrist and finger joints of the affected hand was increased in case 15.

6. Crothers, B.: The Influence of Age upon Ventricular Displacement in the Hemiplegias of Childhood, Tr. Am. Pediat. Soc. **50**:47, 1938. Crothers, B., and Wyatt, G. M.: Mechanism of Displacement of the Ventricular System in Children with Atrophic Lesions, Arch. Neurol. & Psychiat. **45**:246 (Feb.) 1941.

In the majority of the cases the hemiplegic nature of the paresis was not noted until the child began to walk, but in 6 instances paresis of the affected leg was observed between the ages of 7 days and 1 year. Paralysis was never as marked in the legs as in the arms and was described by the parents in some such way as "when he was about 6 months old I noticed he didn't kick his right leg as much as his left in his bath." The patient in case 15 had obvious weakness of the muscles of the right side of the trunk and the right leg, but he could move the right leg, although not as freely as the left one, and on examination its musculature felt hypotonic, with an abnormally large range of passive movement at the ankle. Paresis of the leg in hemiplegias of early infancy is apt to be mild and is perhaps best described as reflecting a disinclination on the part of the infant to use the affected leg as much

Fig. 2 (case 15).—Enlargement from motion picture film, showing increase of passive movement at the left ankle.

as the normal one. Consequently, the disability of the leg is easily overlooked by the examining physician, though the parents may be aware of it.

The age at which spasticity supervened in these infants is difficult to determine. (For the purposes of this article spasticity is defined as increased resistance to passive movement, with increased reflexes and a tendency to contractures. Sometimes one factor and sometimes another of this triad dominates the clinical picture and may be accompanied by atrophy of the affected side, clonus at various joints and Babinski's sign.) Two children were not seen after the initial examination until they were 5 and 4½ years old, respectively, and by this time both of them showed typical spastic hemiplegia.

Intramuscular treatment for syphilis so terrorized the tenth patient that it was not possible either to examine her adequately or to observe

her behavior until she was 3 years old, when it was suddenly realized that she had hemiplegia. The infant from whom a subdural hematoma was removed at 12 days of age is now a year old and appears normal.

There remained 12 patients observed sufficiently frequently and critically to suggest that some relation existed between the onset of spasticity and the age of the child. The earliest observation was made on a patient 6 months of age (case 7), at which time the patient, who had had a severe umbilical hemorrhage on the second day of life, showed hemiplegia, with increased tendon reflexes and a unilateral Babinski sign but no increase in resistance to passive movement. This child was not seen again until he was 2 years old, at which time mild spastic hemiplegia was said to be present. His mother has not brought him to be examined for two years as she considers him well. The patient in case 4 had a flaccid arm and spastic legs and retained tonic neck reflexes at 10 months of age. At 4 years of age he had generalized disorganization of motor control, with mixed hypertonia and hypotonia and evidently a widespread cerebral lesion which affected the motor control of the hypotonic left arm more than that of the other extremities. The remaining 10 patients exhibited spasticity between the ages of 1 and 2½ years.

The large proportion of patients who showed paresis of the face is of further interest. Kennard [1d] observed that in cases of congenital and neonatal hemiplegia in human infants the face frequently is not involved, probably because its motivation subsequent to injury is undertaken from other than the usual cortical areas. Her observations suggest that either the present series includes a number of patients with unusually widespread lesions or the lesions occurred at a considerable time after birth. There were 6 cases in which there was facial involvement. The patient in case 1 was noted to have a weak arm at 3 months and hemiplegia involving the face at 2½ years of age. The encephalogram demonstrated the type of change seen only in lesions acquired early in life. The patient in case 3 had a weak arm at birth and when seen again, at 5 years of age, had spastic hemiplegia. The patient in case 8 had a weak arm twenty-four hours after delivery and spastic hemiplegia at 1 year of age. The patient in case 9 had a weak hand and arm at 3 days, and hemiplegia at 2½ years of age. The patient in case 14 had a weak arm at 2 weeks and hemiplegia at 2½ years of age. The patient in case 15 had a weak arm at 3 months and hemiplegia at 14 months of age. In a general way selection of cases by the presence of facial paralysis gave substantially a list of those in which weakness of the arm was noted early, the only exceptions being case 2, in which weakness was noted when the patient was 3 days old and in which facial weakness was said not to exist, and case 6, in which

weakness was noted when the patient was about 2 or 3 months of age and in which there was no mention of the condition of the face.

COMMENT

A group of 15 infants early in life showed paresis of one arm, the hypotonia being so pronounced that in several instances trained observers had made a diagnosis of brachial palsy although the disability was actually due to cerebral lesions. In 14 instances the evidence that the injury was cerebral depended on the development of spastic cerebral palsies, which in all but 1 case progressed to hemiplegia later in life. The drainage and removal of subdural collections of fluid in case 15 were followed by relief of the symptoms.

The results of various pathologic and physiologic studies made previously by other investigators help to explain the present observations. McNutt described the cases of 2 infants who exhibited weakness of an arm and convulsions and who on autopsy were shown to have unilateral hemorrhages over the cortex; in case 15 operation disclosed a lesion similar to those she described.

There is a certain parallelism between the observations in the present clinical cases and those of Kennard on infant monkeys and chimpanzees. In her animals lesions limited to the motor and premotor cortical areas produced few motor changes early in infancy, but as the infants developed motor disturbances appeared, first as paresis and much later as spasticity. More extensive experimental decortications resulted in pronounced paresis and spasticity earlier than those produced by lesions limited to the motor cortex. By analogy, it seems likely that cortical lesions are responsible for the same sequence of events in human infants. Moreover, involvement of the face in most of the cases in which paresis appeared early suggests that marked, early appearing paresis is the result of extensive cortical lesions.

In certain of the present series of cases the evidence suggests that the lesions were not confined to the cortex. In case 4 tetraplegia developed, with mixed flaccidity and spasticity, presumably the result of diffuse lesions which involved both hemispheres widely. The encephalogram in case 1 suggested that there was rather generalized atrophy of the involved hemispheres. The involvement of subcortical structures may have been the cause of variations in the time at which spasticity appeared, for in some infants it did appear sooner than one would anticipate, judging by Kennard's results. Phylogenetic differences between monkeys and chimpanzees, on the one hand, and human infants, on the other, may have some bearing on the discrepancies.

Attempts to relate the appearance of spasticity to myelination of the tracts alone appeared unsatisfactory because of lack of detailed knowledge

about the extent of the lesions present. In addition, the process of myelination is complicated. A period often measured in years intervenes between the onset of myelination and its completion in certain tracts. While the appearance of myelin in the tracts of the normal intact person follows a schedule in a general way related to the phyletic age, it is possible to cause variations in the schedule. According to Langworthy,[7] Flechsig found that the optic nerves and tracts of an infant born two months before term and dying one month after birth showed more advanced myelination than did the same tracts in a full term normal infant who had died at birth and therefore was one postconceptional month older than the premature baby. According to Langworthy,[7] myelination in the optic nerves and the radiations related to one eye of a newborn kitten can be prevented by suturing the eyelids of that eye shut at birth, while the normal process will go on in the tracts related to the other eye. Use thus seems to have at least some influence on the process. It seems that in order to relate the evolution of hemiplegias in infancy to myelination it would be necessary to study the process in persons with hemiplegia.

The mildness of the paresis of the leg in the paretic stage of hemiplegia should be stressed. Since the paresis is not accompanied by reflex changes and is simply a failure of use, it is seldom noted unless the infant's spontaneous movements are observed carefully. Increased range of motion in the distal joints and hypotonia on palpation may also be present. The same may be true of the arm of patients with the milder lesions. It is probable that more careful observation of young infants will disclose more patients with the early phase of the syndrome and thus increase the opportunities for determining the acute pathologic changes. Patients with mild lesions who recover spontaneously will in all probability be encountered, and the need for thoroughgoing understanding of the pathologic mechanism will thus be made more definite.

SUMMARY

The evolution of hemiplegias in infancy has been described. In early infancy weakness and hypotonia are the outstanding signs. They tend to be most marked at an interval of days, weeks or months after birth, are more obvious in the hand and the arm than in the foot and the leg and are least pronounced in the musculature of the trunk. When the involvement is mild these signs take the form of a disinclination on the part of the infant to use the extremities. It seems likely that mild

7. Langworthy, O. R.: Development of Behavior Patterns and Myelinization of the Nervous System in the Human Fetus and Infant, Contrib. Embryol. (no. 134) **24**:1, 1933.

early symptoms of this syndrome easily escape attention, but it is also probable that relatively circumscribed lesions of the cortex of the newborn infant produce no observable changes.

In the latter half of infancy paresis is replaced by spasticity or spasticity appears without previous overt involvement, with all the well recognized neurologic signs and symptoms of cerebral motor disturbance.

The sequence of weakness and hypotonia followed by spasticity occurs as the result of damage to the infantile cortex. The observations of Kennard offer support for such an interpretation. Processes of gradual maturation going on in the brain as a whole are probably responsible for the progressive changes.

VASCULAR ANOMALIES OF THE SPINAL CORD IN CHILDREN

DOUGLAS N. BUCHANAN, M.D.
AND
A. EARL WALKER, M.D.
CHICAGO

Vascular anomalies of the nervous system are not unusual, but such abnormalities of the spinal cord especially in children are seldom seen. If 15 years of age is considered the upper limit of childhood, only 3 cases of vascular anomalies of the spinal cord in children have been found in the literature. The earliest is the well known case reported by Cobb [1] from the clinic of Harvey Cushing.

RÉSUMÉ OF CASES FROM THE LITERATURE

CASE 1 (Cobb [1]).—An 8 year old boy suddenly experienced a severe pain in the lower part of the back radiating into the lower part of the abdomen. He felt weak, became nauseated and vomited. After resting at home for four days he returned to school, but three days later he experienced the same pain again. He rolled about in agony. As the pain eased his left foot felt numb, and the numness gradually spread up the leg to the thigh and down the opposite leg. Within fourteen hours of the onset of the second attack both legs were paralyzed and insensitive. The sphincters of the urinary bladder and the rectum were also paralyzed.

Gradually the flaccid limbs became spastic and priapism developed. Dr. Cushing saw the boy and called attention to several port wine nevi about the lower part of the abdomen just below the upper level of anesthesia, at the tenth thoracic segment. He operated and exposed a tangled mass of huge pulsating vessels which filled the spinal canal in the lower thoracic region. Although a decompression was left, no improvement occurred.

CASE 2 (Blahd [2]).—A 14 year old boy suddenly experienced a severe pain in the groin, which lasted a few minutes. He was apparently well for a few months; then a similar pain occurred. Nine months after the first attack a third, and more severe, pain was experienced, and within nine hours he became completely paralyzed below the waist. The lower extremities were flaccid, and there was a sensory level at the eleventh thoracic dermatome.

Laminectomy was performed, and in the lower thoracic region a mass of large veins was found compressing the spinal cord. Decompression gave no relief.

From the Departments of Pediatrics and Surgery, University of Chicago.

1. Cobb, S.: Haemangioma of the Spinal Cord, Associated with Skin Naevi of the Same Metamere, Ann. Surg. **62**:641-649, 1915.

2. Blahd, M. E.: Hemangioma of the Spinal Cord, J. A. M. A. **80**:1452-1453 (May 19) 1923.

CASE 3 (Black and Faber [3]).—A boy 9 years of age after undergoing tonsillectomy complained of lumbar pain. He walked bent over like an old man. He had severe bouts of sciatic pain. Neurologic examination revealed that both knee jerks were absent although the ankle jerks were lively. Both plantar reflexes were extensor. The appreciation of pinprick and temperature was impaired below the eleventh thoracic dermatome.

Lumbar puncture revealed xanthochromic spinal fluid, which spontaneously coagulated. The dynamics were normal at first, but after 5 cc. of spinal fluid was removed jugular compression did not produce an increase in spinal fluid pressure.

Laminectomy of the ninth, tenth and eleventh thoracic vertebrae was performed by Dr. E. B. Towne. On opening the dura mater numerous tortuous blood vessels were seen on and piercing the spinal cord. The patient was given roentgen therapy, and his condition improved temporarily. In the course of a few months he experienced sudden recurrences of his weakness, with slight improvement between each episode. After the last episode he had complete flaccid paralysis, with absence of the deep reflexes, muscular atrophy of the legs and edema of the ankles. The sensory disturbances were slight. Roentgenograms made after intrathecal injection of iodized poppyseed oil demonstrated a block at the second lumbar vertebra. The laminas of the twelfth thoracic and first, second and third lumbar vertebrae were removed by Dr. Towne at a second operation. A reddish mass extending to the second lumbar vertebra distended the intrathecal space, but no varices were seen. Subsequent roentgen therapy produced only slight improvement.

REPORT OF AN ADDITIONAL CASE

J. D'A., a 3 year old boy, was admitted to the University of Chicago Clinics on May 7, 1940 because of stiffness and pain in the back for the previous month. He had been born spontaneously at full term. He was the tenth child in the family, all of whom were alive and well except one boy who had died of pneumonia at 4 months of age. The patient's development was normal. Walking began when he was 13 months old. His present complaints began about a month prior to admission. The child awoke one night complaining of abdominal pain, which his mother thought was due to his back, for he complained when it was touched or manipulated. The pain lasted a few minutes and recurred every few hours. It was unrelated to the taking of food, and the patient had no gastrointestinal disturbance except slight constipation. Between attacks he was perfectly well.

Physical and neurologic examinations revealed no abnormality except that he walked with his back rigid and slightly flexed. Roentgenograms of the spine demonstrated no pathologic condition. The mother refused to permit a lumbar puncture and took the child home before the examination could be completed.

Second Admsision.—On September 6 the child was brought back to the hospital. His legs had become so weak that about a month after leaving the hospital he was unable to walk. He had entered another hospital, but as his condition was progressing he was transferred to the Bobs Roberts Memorial Hospital for children. He complained of severe pain in the neck, back and legs, which was aggravated by movements of the body.

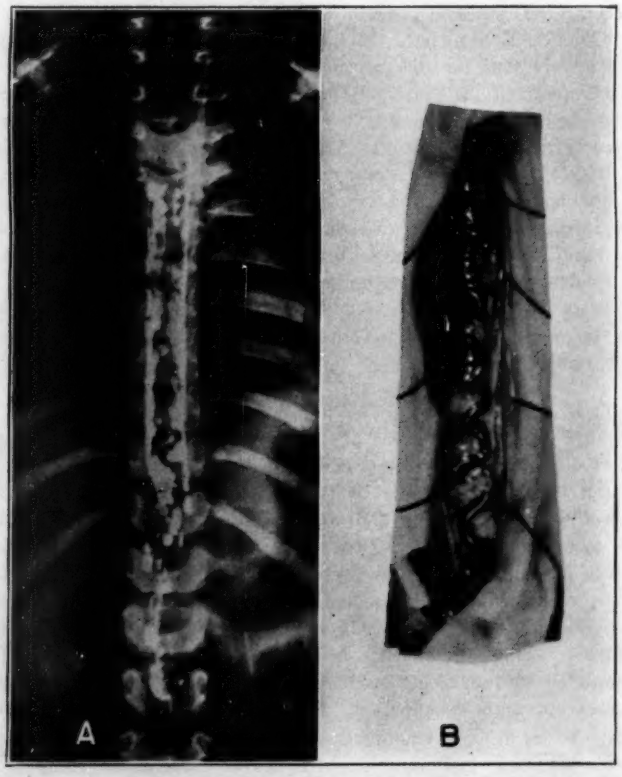
Examination: The patient was irritable and unable to sit alone. His head was held stiffly, and any attempt to move his neck was resisted.

---

3. Black, W. C., and Faber, H. K.: Blood Vessel Tumor of the Spinal Cord in a Boy Aged Nine Years, with Special Reference to a New Diagnostic Syndrome, J. A. M. A. **104**:1889-1890 (May 25) 1935.

The cranial nerves were normal. He could move his arms freely through a normal range without apparent weakness or ataxia. The child responded well to pinprick on both the arms and the legs. Position sense of the fingers and toes was normal. He could move his feet feebly. Both knees could be weakly extended but not flexed. No movement was possible at the hips. Passive manipulation of the legs disclosed an extensor hypertonia of the jackknife type.

The tendon reflexes were extremely lively in both the upper and the lower extremities, and ankle clonus was present bilaterally. Both plantar reflexes were extensor. The abdominal reflexes were absent.



A, the myelogram made after the intrathecal injection of 2 cc. of iodized poppy-seed oil in the lumbar region. The roentgenogram was taken after the patient had been head down on a tilting fluoroscopic table for ten minutes. *B*, the lesion as seen at operation.

There were no cutaneous nevi or pigmented spots on any part of his body.

The clinical diagnosis was intramedullary tumor of the spinal cord extending from the lumbar to the cervical segments.

Lumbar puncture was performed. The initial pressure of 90 mm. of spinal fluid was not increased by jugular compression. The spinal fluid was xanthochromic and coagulated spontaneously. An insufficient amount was collected for quantitative determination of the protein content. Two cubic centimeters of iodized

poppyseed oil was injected into the subarachnoid space, and the spine was examined under the fluoroscope. The oil was seen to streak irregularly about the spinal cord to the eighth thoracic vertebra (*A* of figure).

Operation: On September 14, with the patient under ether anesthesia, laminectomy of the third to the twelfth thoracic vertebrae was performed. The epidural fat was decreased. When the dura mater was opened a number of large tortuous vessels were seen zigzagging across the posterior surface of the swollen spinal cord. The majority were dusky red, but some were smaller and bright red (*B* of figure). In several places the vessels could be seen to pierce the surface of the spinal cord. No attempt was made to coagulate or to remove them. Since there was no tension on the dura, it was closed and the muscles approximated with black silk sutures.

Course: The patient had an uneventful convalescence. On the fourteenth postoperative day roentgen therapy was started. In divided doses through two portals 840 r was delivered to the cervical portion and 960 r to the thoracic portion of the spinal cord. The patient was discharged on September 30. Although the paralysis of the lower extremities did not regress, the patient suffered no pain after the operation and seemed comfortable.

Diagnosis.—The lesion in this case was obviously an extensive vascular anomaly of the spinal cord, which probably extended from the lumbar portion to the upper cervical region of the spinal cord, since the patient exhibited a stiff neck and exaggerated reflexes in the arms. The precise nature of the lesion was indeterminable without causing further damage to the spinal cord. It might be classed as a varix, yet a complete study of the spinal cord might show more extensive vascular anomalies, which would justify the term hemangioma, or even a true neoplasm—a hemangioblastoma.

COMMENT

Analysis of 4 cases of the vascular anomalies of the spinal cord in childhood yields fairly consistent data. It is interesting that in all 4 cases the patient was a boy. Whether this sex incidence is merely the result of the smallness of the series or indicates a true predilection of the tumors for the male of the species cannot be stated at this time. The onset of symptoms is typically sudden, and in all cases excruciating pain is characteristic. It is interesting that the pain in 3 cases was abdominal and in the fourth sciatic, a corollary to the fact that the lesions occurred in the lower thoracic or lumbar region. The severe pain recurs periodically and is followed after a short or long interval by weakness of the legs. The pathogenesis of the severe paroxysmal pain cannot be ascertained from any of these cases since none of the patients has come to autopsy. However, in a patient aged 16 years [4] in whom the presence of the tumor was announced by severe pain, a laminated clot was found in the spinal cord. It is likely that small repeated hemorrhages are the cause of the paroxysmal attacks of pain. When the hemorrhage has progressed to such a size as to cause compression or, by infiltration, to produce destruction of the spinal cord, paretic

4. Robertson, E. G.: A Case of Arterial Angioma of the Spinal Cord, M. J. Australia **2**:384-385, 1938.

symptoms develop, the motor phenomena being much more pronounced than the sensory.

The typical history of a child with a vascular anomaly of the spinal cord reads like this. In a boy 8 or 9 years of age and in perfect health, agonizing pain in the back radiating into the lower part of the abdomen suddenly develops. In a few hours the pain subsides and the patient is apparently normal. After a few weeks a similar episode occurs and lasts a short time, following which the boy walks with a stiff back and slightly bent forward. After one or two more episodes of similar type the legs become weak and the patient has difficulty in walking.

Examination discloses a stiff back and spastic paresis of the legs, with indefinite sensory disturbances. Lumbar puncture reveals a complete block with xanthochromic fluid of high protein content.

Myelographic Characteristics.—It has been said that the myelogram of a patient with a vascular anomaly of the spinal cord made after the injection of iodized poppy seed oil is characteristic. Certainly the myelogram does not resemble that of a patient with an intramedullary tumor of the spinal cord. We cannot concur with the opinion that it is pathognomonic, for we have seen myelograms similar to that of the patient in the present case which were taken of patients with adhesive arachnoiditis of the spinal cord.

Therapy.—No adequate treatment has yet been devised. Any attempt at removal of the lesion results in ischemic myelopathy. Decompression of the cord in many cases is not necessary, and even when pressure may exist the procedure does not seem to be effective. Roentgen therapy has been tried without success. If severe pain persists, chordotomy may afford amelioration.

Pathologic Classification.—To classify these tumors pathologically on the basis of their appearance at operation seems to us to be extremely difficult, if not impossible, and the variety of names applied to these lesions substantiates this view. Only when the entire cord can be studied grossly and microscopically is it possible to say whether a given lesion should be classified as a varix, a hemangioma or a hemangioblastoma. On inspection of a small area on the posterior surface of the spinal cord the three types of lesion may appear similar. For that reason we believe that these lesions should merely be called vascular anomalies until their true nature can be determined by microscopic study.

SUMMARY

Vascular anomalies of the spinal cord in children are rare, but the patients have a fairly uniform clinical history. These abnormalities do not respond to any form of therapy. Pathologic classification of the lesions cannot be made by gross inspection at operation.

DEVELOPMENT OF THE FETAL LUNG

WITH SPECIAL REFERENCE TO THE LINING OF THE ALVEOLI AND THE EFFECT OF IMMATURITY ON RESPIRATION

ROBERT F. NORRIS, M.D.
PHILADELPHIA

THOMAS T. KOCHENDERFER, M.D.
NORRISTOWN, PA.
AND
RALPH M. TYSON, M.D.
PHILADELPHIA

For a number of years we have been struck by the absence of truly pathologic lesions as a cause of death among many of the immature infants born in the Pennsylvania Hospital. Many of these infants appeared to have died of respiratory failure, as evidenced by cyanosis and gasping respirations in the presence of seemingly normal cardiac function. In fact, it was usual for the heart to continue beating even after respirations had ceased. Numerous embryologic studies on the development of the fetal lung and the lining of the alveoli have been made; yet in the literature there has been little discussion of the clinical significance of the results of such studies. Although death in the premature infant is undoubtedly caused by a complex mechanism which includes anatomic and metabolic dysfunction of numerous organs, it seemed desirable to make an anatomic study of the fetal lung to determine what bearing immaturity might have on respiratory failure.

MATERIAL AND METHODS

Twenty-two infants who either were dead or died within twenty-two days of birth were selected for study. None of the stillborn infants were macerated and so far as could be determined, all died during labor. It was estimated that the infants, whose crown to heel measurements ranged from 15 to 53 cm., varied in age from 4 lunar months to full term. At necropsy the thoracic cavity was opened and the right main bronchus was occluded by a ligature. Through a soft rubber catheter, inserted by way of the trachea into the left main bronchus, a 10 per cent concentration of solution of formaldehyde U. S. P. was allowed to flow by gravity until the lung filled the left thoracic cavity. The pressure of the injected fluid in no instance exceeded 20 cm. of water. As the catheter was removed the main bronchus was

This work was aided by a grant from Mead Johnson & Co.

From the Ayer Clinical Laboratory and the Pediatric Service of the Pennsylvania Hospital.

ligated to insure fixation in the expanded position. Both lungs were then immersed in Regaud's solution for at least forty-eight hours. The blocks were embedded in paraffin, and for ordinary studies sections were cut at a thickness of 5 microns and stained with hematoxylin and eosin.

Segments of the injected lungs of 3 fetuses which were 15, 25 and 48 cm. long, respectively, were reconstructed in drawings. This was accomplished as follows: Images of serial sections, 10 microns in thickness, were projected on a screen at such a magnification that 10 microns on the section was equal to 0.1 inch (2.5 mm.) on the screen. Tracings of the desired respiratory structures were made for each section. The horizontal diameters of each structure were measured, and marks indicating the limits of each diameter were transferred to a single sheet of 0.1 inch graph paper. On the graph paper the horizontal diameter of the respiratory elements of each microscopic section were thus superimposed vertically on one another at 0.1 inch intervals in much the same manner as that employed in wax plate reconstructions. The images produced were therefore accurate to scale for two dimensions. The contours of these structures were then traced on drawing paper, and by taking into account the unplotted third dimensions the illustrative drawings were made.

RESULTS AND COMMENT

The respiratory portion of the fetal lung originates from the endoderm of the primitive gut. The anlages of the two lungs are a pair of epithelial buds which grow into the surrounding mesoderm and, together with this investment of mesoderm and its covering of mesothelium, come to lie in the pleural cavities. By repeated dichotomous and monopodial branching of the bronchi, bronchioles and terminal air spaces, the structure of the mature lung is established at about the time of birth. Since there is no evidence that continued division of the terminal air spaces occurs for an extended period after birth, enlargement of these air spaces must be the chief means by which the volume of the lung keeps pace with the growth of the body. The growth and expansion of the air spaces are probably facilitated by the increase in the elastic tissue of the septums, which is accelerated late in fetal life and continues to maturity (Staemmler,[1] Klemola [2] and Amprino and Ceresa [3]).

---

1. Staemmler, M.: Die Bedeutung der elastischen Fasern in den Lungenalveolen von Neugeborenen für Klinik und gerichtlich-medizinische Beurteilung, Deutsche Ztschr. f. d. ges. gerichtl. Med. **25**:202, 1935.

2. Klemola, E.: Ueber den Lungenbau der Frühgeburt und des ausgetragenen Kindes, vor allem mit Rücksicht auf die Entwicklung der elastischen Fasern und der Kapillaren (Vorläufige Mitteilung), Acta pædiat. **21**:236, 1937.

3. Amprino, R., and Ceresa, F.: Transformazioni nella struttura del polmone nel periodo postnatale e senile, Arch. ital. di anat. e di embriol. **38**:428, 1937. Amprino, R.: Come si forme e come si organizza la struttura del polmone nel periodo fatale, ibid. **38**:447, 1937.

Extensive reviews on the embryonic development and the anatomy of the lung may be found in the works of Grosser,[4] Miller[5] and Grethmann.[6]

In our reconstructions of the terminal bronchioles and their respiratory elements of fetuses 15, 25 and 48 cm. in length (figs. 1, 2 and 3), it will be seen that the complexity of the lung structure progressively increases with age. With a body length of 15 cm. (fig. 1) the terminal respiratory elements are relatively large and blunt ending. With a body

Fig. 1.—Reconstruction of the lung of a 15 cm. fetus. The localized cystic dilatations and globular character of the terminal air sacs are particularly noteworthy.

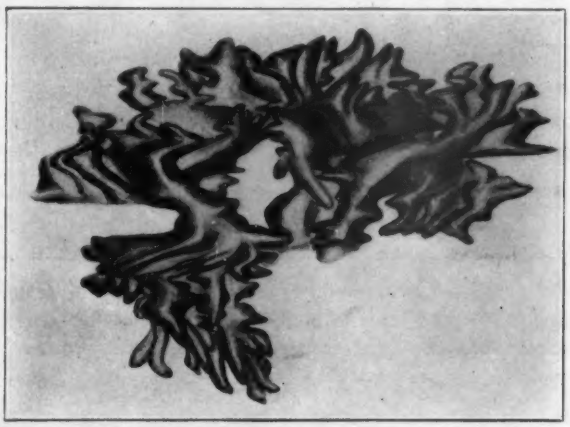


Fig. 2.—Reconstruction of the lung of a 25 cm. fetus. The increased complexity is accompanied by a decrease in the size of the terminal air sacs.

4. Grosser, O.: The Development of the Pharynx and of the Organs of Respiration, in Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, pp. 446-497.

5. Miller, W. S.: The Lung, London, Baillière, Tindall & Cox, 1937.

6. Grethmann, W.: The Architecture of the Terminal Sections of the Bronchi of the Human Lung: The Pulmonary Acinus, Am. Rev. Tuberc. **31**:261 (March) 1935.

length of 25 cm. (fig. 2) the terminal branches are still slender but appear to be comparatively smaller. With a body length of 48 cm., at the time of birth (fig. 3), however, many of the distal respiratory elements are globular and have the bottle-shaped appearance said to be characteristic of the mature alveolus.

It is obvious that branching of the distal elements does not ordinarily occur in a symmetric or dichotomous manner. The reconstructions therefore do not support the view of Grethmann [6] that even the terminal air spaces develop by dichotomous branching, but rather are in agreement with the belief expressed by Miller [5] that a combination of

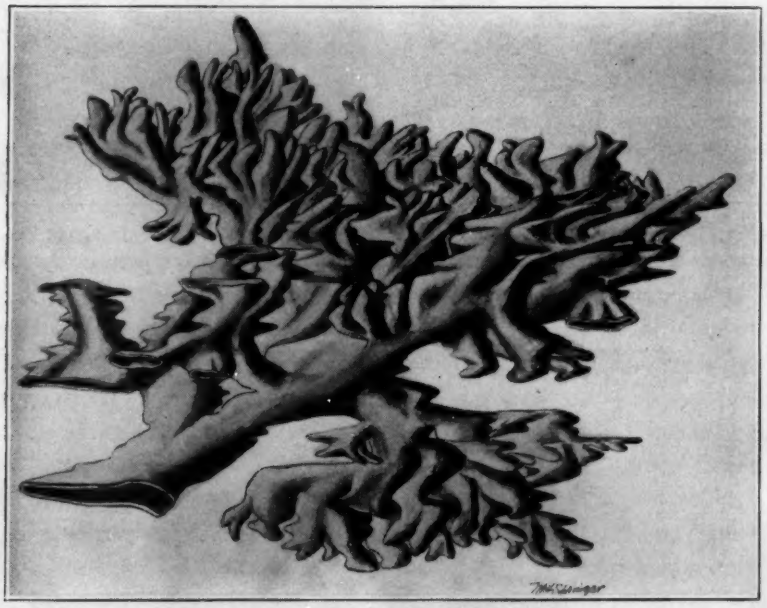


Fig. 3.—Reconstruction of the lung of a 48 cm. fetus. The pattern present at birth is attained. The tendencies to globular dilatation of the subterminal alveoli and to unequal subdivision of the respiratory elements are apparent.

dichotomous and monopodial branching occurs. Asymmetric branching of the lung is a logical assumption, since the comparatively rigid walls of the pleural cavity might well inhibit uniform or symmetric branching of the respiratory elements.

In the model of the 48 cm. fetus (fig. 3) the structure of the recurrent respiratory bronchiole in the right lower quadrant of the reconstruction is most readily distinguished. A maximum of four separate subdivisions may be seen distal to the respiratory bronchiole. If Miller's terminology is followed these are, in succession from the periphery, the pulmonary alveoli, the alveolar sacs, the atria, the alveolar ducts and, finally, the respiratory bronchiole. Although Grethmann [6] has expressed

himself as unconvinced that the atria of Miller are normally present, these structures are apparent in our reconstruction. Furthermore, Husten [7] has found three generations of respiratory bronchioles and Grethmann [6] only two. Our reconstructions again support Miller in that the number of generations of respiratory bronchioles is variable. The controversy on these points, and others which have confused the literature, may well have been caused by the apparent failure of all elements of the respiratory portion of the lung to attain the same number of subdivisions. In fact, it seems evident from the reconstruction of the mature lung (fig. 3) that at the time of birth many of the respiratory elements are by no means equally subdivided. Even in the lower right recurrent bronchiole (fig. 3) the terminal branches are not all of the same generation. Some appear to end with alveolar sacs and others with atria. In the reconstructions of the immature lungs (figs. 1 and 2) subdivision has not progressed so far and the number of generations of respiratory passages appears more uniform. If these observations are correct, many elements of the developing bronchial tree are prevented from undergoing the same number of subdivisions as others by the limitations of the pleural cavity. This tendency to unequal subdivision, therefore, might well be more evident in the mature than in the immature lung.

To the left of the large bronchiole, in about the middle of the reconstruction of the 15 cm. fetus (fig. 1), is a large, terminal, dilated and subdivided structure attached to the bronchiole by a single undilated tubule. It is entirely possible that an artefact may have been responsible for this peculiarity. For example, focal dilatation may have been caused post mortem by the injection of the lung. But the presence of a long-drawn-out, blindly ending tubule at the extreme left of the model is against this view, while it may represent a similar connecting tubule the dilated distal segment of which became detached ante mortem. Such an explanation would seem far fetched were it not for the reports of Kampmeier [8] that early generations of uriniferous tubules and their glomeruli are normally provisional in the fetal kidney. These elements become isolated and slightly cystic before eventual degeneration and disappearance. It has also been suggested by Norris and Herman [9] that an abnormal continuation of this process in the kidneys and other organs might explain the occurrence of polycystic disease of these organs. Such an overproduction of respiratory elements, with subsequent reduc-

7. Husten, K.: Ueber den Lungenacinus und den Sitz der acinösen phthisischen Prozesse, Beitr. z. path. Anat. u. z. allg. Path. **68**:496, 1921.

8. Kampmeier, O. F.: The Metanephros or So-Called Permanent Kidney in Part Provisional and Vestigial, Anat. Rec. **33**:115 (June) 1926.

9. Norris, R. F., and Herman, L.: Observations on the Anatomic Basis of Congenital Polycystic Kidneys, Tr. Am. A. Genito-Urin. Surgeons **31**:41, 1938; The Pathogenesis of Polycystic Kidneys, to be published.

tion, may also occur in the lungs, both as normal and as abnormal phenomena. Since we have not as yet observed these peculiarities in other fetuses, the focal dilatations of the respiratory elements in the present case may simply be developmental anomalies. However, it is possible that in the normal development of the lung there is not only unequal subdivision of the respiratory elements but eventual degeneration and disappearance of some of them.

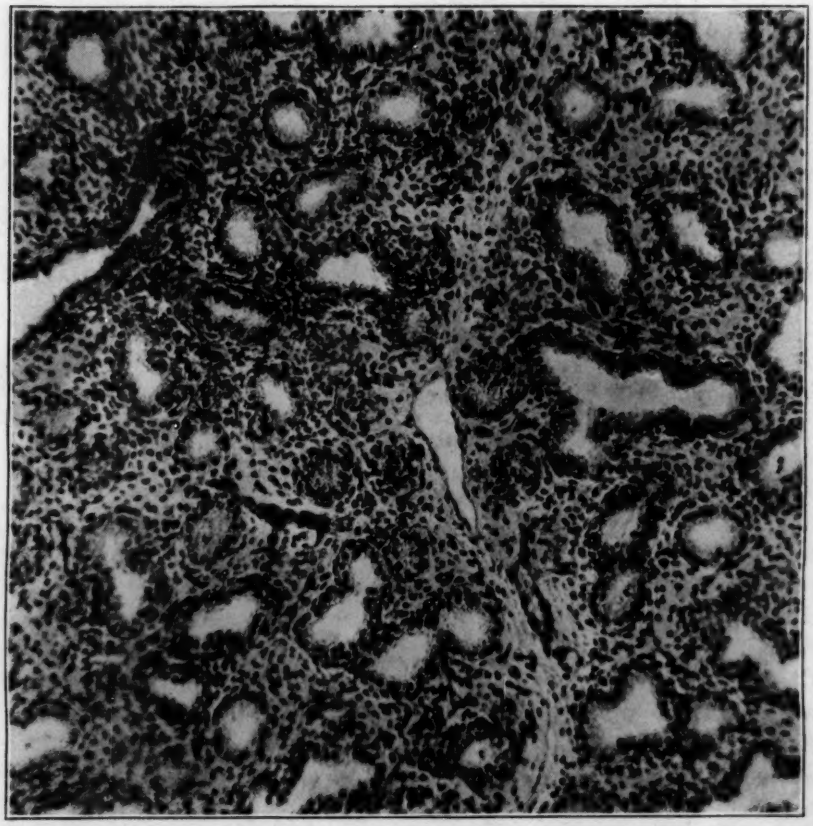


Fig. 4.—Section of the lung of a 15 cm. fetus. The primitive air sacs are still glandular and are obviously lined by epithelium. The intervening stroma is loose and comparatively avascular.

Microscopically, at the 15 cm. stage (fig. 4) the parenchyma of the lung is composed of circular, glandlike primitive air sacs [10] which are

10. Hereafter the term "air sac" will be used as a general term for any portion of the bronchial tree lying distal to the respiratory bronchioles. Similarly, in the discussion of the mature lung and the lungs of infants after birth, the term "alveoli" will be used according to custom for all such respiratory spaces. In routine sections these structures can rarely be otherwise identified.

widely spaced in a mesenchyma of blood vessels and fetal connective tissue. These air sacs are lined by a single layer of low cuboidal epithelial cells, with clear cytoplasm and centrally or basally located nuclei. The epithelial lining of the air sacs is continuous with the epithelium of the bronchioles. The separation of these air sacs by loose stroma and their circular shape on cross section may indicate that growth

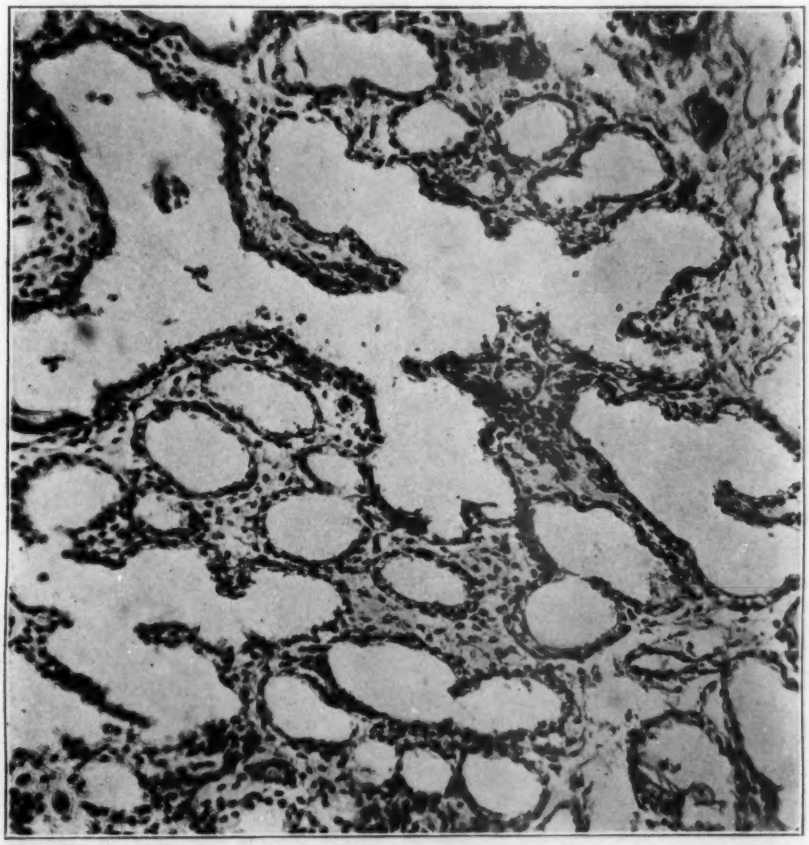


Fig. 5.—Section of the lung of a 25 cm. fetus. The air sacs are still lined by continuous sheets of epithelium, but the fetal mesenchyma is greatly diminished.

and subdivision are not yet impeded by the limitations of the pleural cavity.

In the section of the 25 cm. fetus (fig. 5) there has been a conspicuous reduction in the amount of stroma between the air sacs, and by repeated subdivision their number has been greatly increased. The epithelial lining, which is for the most part continuous, is now definitely cuboidal or flat. The vascularity of the stroma appears to be greater, perhaps because the fetal connective tissue is relatively less abundant.

In the 35 cm. fetus (fig. 6) a further subdivision of the air sacs is apparent, and the masses of fetal connective tissue which formerly separated them are no longer conspicuous. The walls and septums of the air sacs, however, are thicker than in the mature lung, since a relatively greater amount of connective tissue is still associated with the capillary network. Only occasional air sacs now have an obviously continuous epithelial lining. In most of them small groups of epithelial cells are widely separated by capillary loops bulging into the lumens.

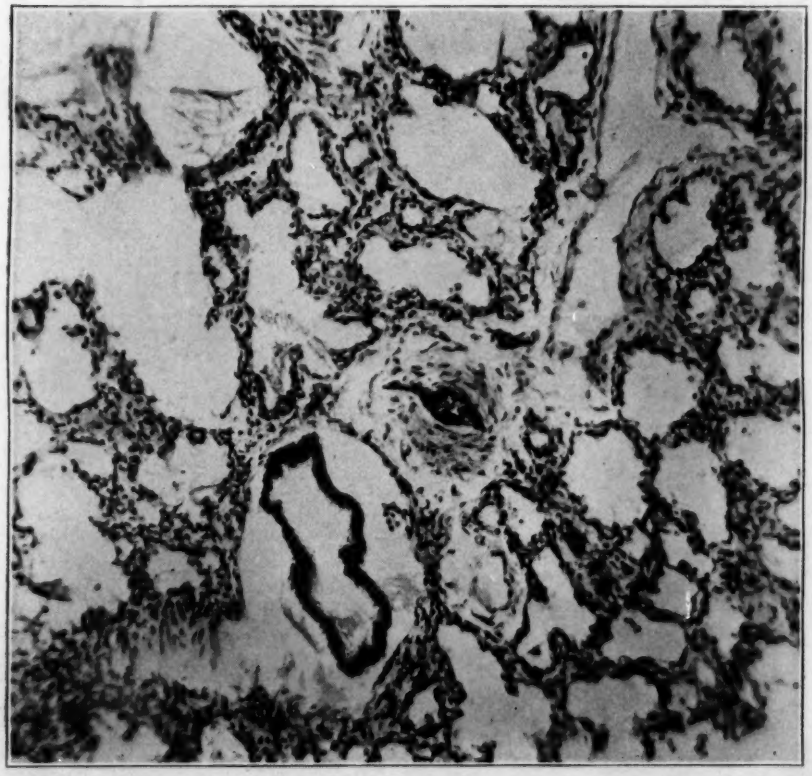


Fig. 6.—Section of the lung of a 35 cm. fetus. With this magnification the scattered epithelial cells in the alveolar walls are scarcely visible. The fetal stroma is much less abundant.

In the 48 cm. fetus (fig. 7) the pattern of the mature lung is attained. The fetal stroma or mesenchyma has disappeared, and complete subdivision of the epithelium-lined tubes has resulted in the large air sacs or alveoli, which are separated from one another only by thin septums containing capillaries. Epithelial cells can no longer be seen, and the capillary walls appear to have no covering between them and the alveolar air.

The lack of vascularity of the entire parenchyma in the lung of the 15 cm. fetus (fig. 4) is striking. To appreciate how few the blood vessels are it is necessary to study the section in a drawing from a higher magnification (fig. 8). Only two small capillaries are present in the stroma between the two air sacs. Furthermore, these vessels are not even in contact with the epithelial cells which line the lumens and of course are not exposed to the interior of the primitive air sacs.

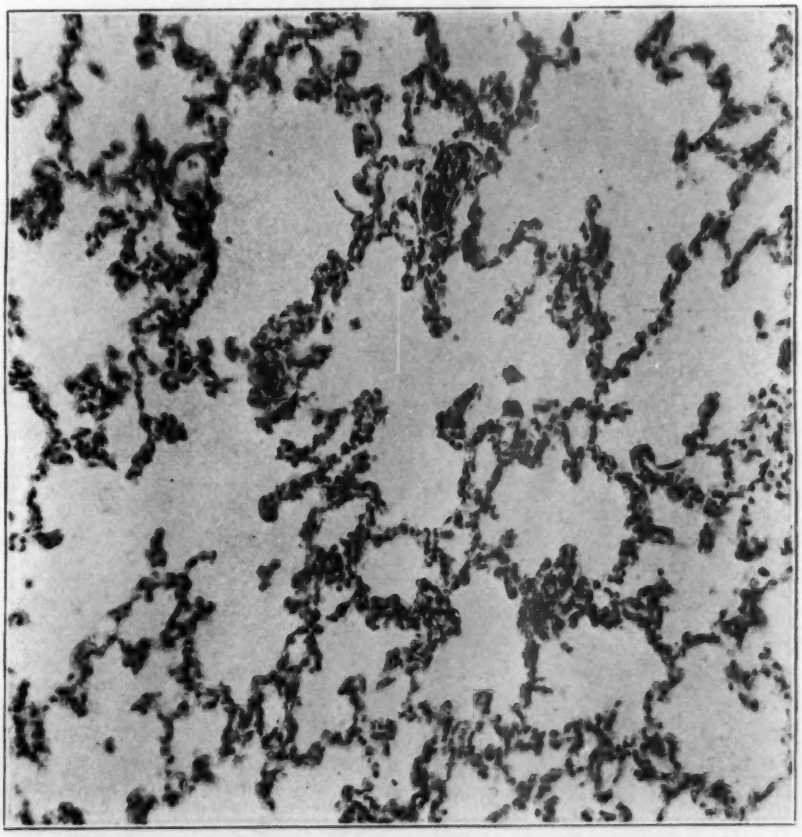


Fig. 7.—Section of the lung of a 48 cm. fetus. At term epithelial cells are no longer visible, and the fetal mesenchyma has disappeared.

In the lung of the 25 cm. fetus (fig. 9) the relative number of capillaries in the stroma has increased. The most important difference, however, is that the capillaries have intruded between and probably replaced the epithelium lining the air sacs. As a result, some of these capillaries in the wall of the air sacs are uncovered by epithelium and are therefore exposed to the potential air space.

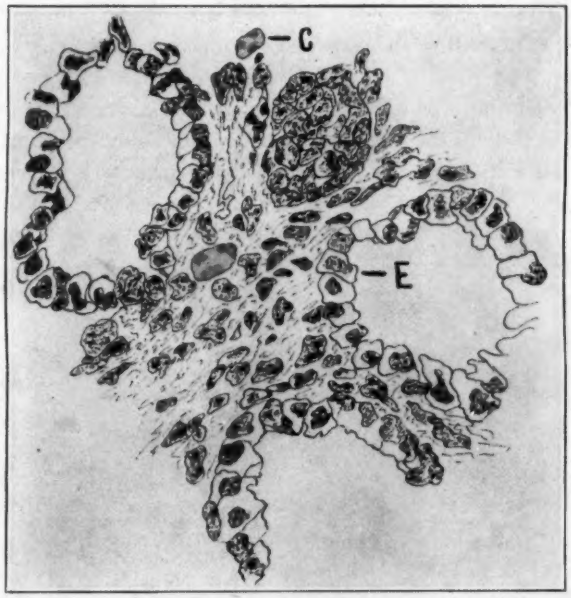


Fig. 8.—Drawing of a highly magnified section of the lung of a 15 cm. fetus. In this and in subsequent figures, *C* signifies capillary and *E* epithelium. The small blood vessels are few and are not located in relation to the potential air spaces.

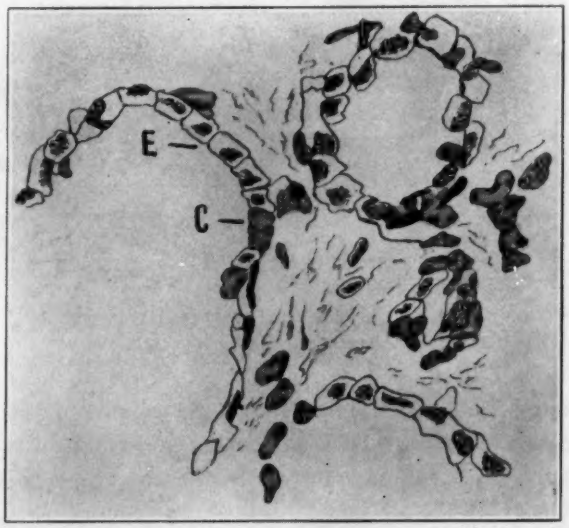


Fig. 9.—Drawing of a highly magnified section of the lung of a 25 cm. fetus. The epithelial cells of the air sacs are being replaced by exposed capillaries.

This invasion of the epithelial lining by capillaries, which has previously been emphasized (Palmer,[11] Barnard and Day [12] and Clements [13]), continues rapidly until, at the 35 cm. stage (fig. 10), capillaries are the most prominent elements of the alveolar walls. Little mesenchymal stroma remains, and only occasional epithelial cells are visible between the exposed capillary loops.

In the fetus at term (fig. 11) no epithelium is visible and the septal or alveolar walls are composed largely of capillaries, with a scanty supporting stroma of connective tissue. With ordinary hematoxylin

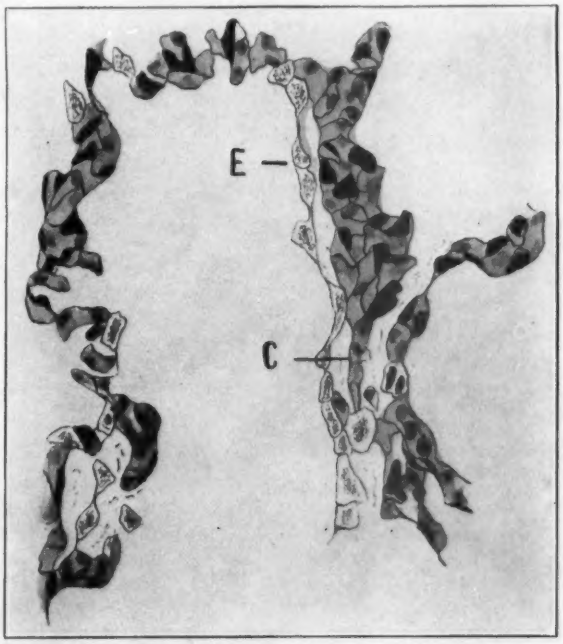


Fig. 10.—Drawing of a highly magnified section of the lung of a 35 cm. fetus. On the right a strip of epithelial cells is being separated from the capillaries of the alveolar wall. On the left only scattered epithelial cells remain.

and eosin stains the capillary endothelium appears to be exposed directly to the alveolar air.

---

11. Palmer, D. M.: (*a*) The Lung of a Human Foetus of 170 mm. C. R. Length, Am. J. Anat. **58**:59 (Jan.) 1936; (*b*) cited by Macklin, C. C.: Pulmonary Alveolar Epithelium: Report of a Round Table Conference, J. Thoracic Surg. **6**:82 (Oct.) 1936.

12. Barnard, W. G., and Day, T. D.: The Development of the Terminal Air Passages of the Human Lung, J. Path. & Bact. **45**:67 (July) 1937.

13. Clements, L. P.: Embryonic Development of the Respiratory Portion of the Pig's Lung, Anat. Rec. **70**:575 (April 25) 1938.

The nature of the lining of the mature air sacs or alveoli is still the subject of much controversy. All investigators agree, however, that in sections stained by ordinary methods the alveolar walls or septums are composed of a rich capillary network associated with small numbers of stromal cells, small amounts of reticulum and ground substance and moderate amounts of elastic tissue. On at least one side the lumens of the capillaries appear to be separated from the alveolar spaces only by endothelium. The ciliated columnar epithelium of the terminal bron-

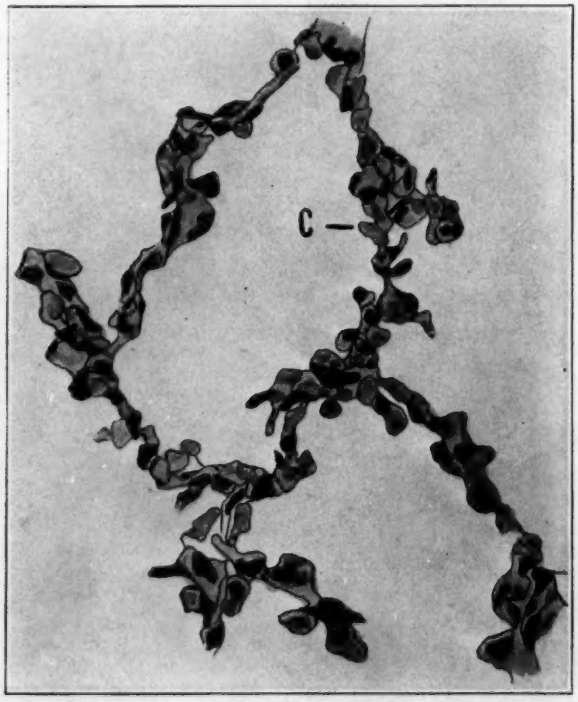


Fig. 11.—Drawing of a highly magnified section of the lung of a 48 cm. fetus. Epithelial cells are no longer visible, and the endothelial cells of the capillaries appear to be exposed directly to the air spaces.

chioles changes into cuboidal epithelium in the respiratory bronchioles. This cuboidal epithelium in any routine section appears to end abruptly at the origin of the alveolar ducts. During the stage of fetal development, however, the early generations of air sacs are also lined with a single layer of cuboidal epithelium similar to that of the respiratory bronchioles. Our results are in agreement with those of Palmer [11] and Barnard and Day,[12] who studied the human lung, and Clements,[13] who studied the lung of the pig. They observed that at about the 25 to 30 cm.

stage the epithelial lining of the air sacs begins to be broken by the intrusion of mesenchymal capillaries between the individual epithelial cells, as shown in our figure 9. At the 35 cm. stage only occasional groups of epithelial cells can be identified in the alveolar walls (fig. 10). At birth solitary epithelial cells may sometimes be observed in the crevices of the capillary network, but thereafter epithelium is no longer visible.

In spite of the fact that epithelial cells normally are not seen in the alveoli of the lung after birth, one group of investigators has expressed the belief that an invisible epithelial lining must be present (Miller,[5] Bensley and Groff,[14] Bremer,[15] El-Gazayerli,[16] Parker and Weiss,[17] Cooper [18] and Ross [19]). It seemed improbable to them that a continued subdivision of the early air sacs could occur in the absence of an epithelial lining. Small collections of epithelial cells, however, persist almost until birth, and it is altogether likely that subdivision of the air sacs ceases at about the same time that the visible epithelial lining disappears. The lining of the alveoli in mammals retains the color of the special stains, notably silver nitrate, which are generally considered specific for epithelium.[14] But the validity of these staining reactions has been seriously questioned (Clements [13] and Josselyn [20]). Furthermore, any one who has had much experience with so-called specific stains realizes how capricious their action may be.

Irritation or inflammation of the lung produced in experimental animals by special methods makes the alveoli appear to be lined by a single layer of cells which looks like cuboidal epithelium and resembles the lining of the respiratory bronchioles.[21] If these cells are true epithelium, they may have proliferated into the alveoli from the respira-

14. Bensley, S. H., and Groff, M. B.: Changes in the Alveolar Epithelium of the Rat at Birth, Anat. Rec. **64**:27 (Dec. 25) 1935. Bensley, R. D., and Bensley, S. H.: Studies of the Lining of the Pulmonary Alveolus of Normal Lungs of Adult Animals, ibid. **64**:41 (Dec. 25) 1935.

15. Bremer, J. L., cited by Macklin, C. C.: Pulmonic Alveolar Epithelium: Report of a Round Table Conference, J. Thoracic Surg. **6**:82 (Oct.) 1936.

16. El-Gazayerli, M.: On the Nature of the Pulmonary Alveolar Lining and the Origin of the Alveolar Phagocyte, J. Path. & Bact. **43**:357 (Sept.) 1936.

17. Parker, F., Jr., and Weiss, S.: The Nature and Significance of Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573 (Sept.) 1936.

18. Cooper, E. R. A.: A Histological Investigation of the Development and Structure of the Human Lung, J. Path. & Bact. **47**:105 (July) 1938.

19. Ross, I. S.: Pulmonary Epithelium and Proliferative Reactions in the Lungs: A Study of the Cellular Response in Lungs After Intratracheal Injection of Toxic and Nontoxic Foreign Substances, Arch. Path. **27**:478 (March) 1939.

20. Josselyn, L. E.: The Nature of the Pulmonary Alveolar Lining, Anat. Rec. **62**:147 (May 25) 1935.

21. El-Gazayerli.[16] Josselyn.[20]

tory bronchioles (Barnard and Day [12] and Sprunt and co-workers [22]). It is not certain, however, that these cells are epithelial. Although they are not so actively phagocytic as cells of the reticuloendothelial system (Cappell [23]), they still may be of connective tissue origin.

In cases of chronic passive congestion and pneumonia in human beings, a similar lining of cuboidal cells may sometimes be seen,[24] and Miller has presented material from such cases to prove the epithelial nature of the alveolar lining. To him the most convincing evidence of such an epithelial lining is the presence, in his material, of isolated sheets of flattened epithelial-like cells lying free in the lumens of the alveoli. These sheets of cells are in a single layer and appear to have been either desquamated or separated from the alveolar walls by fixation. These cells are thought to be normally present but invisible. Swelling caused by pneumonia or chronic passive congestion makes them visible. There are several objections to this theory. In the first place, these cells are visible in by no means all cases of pneumonia and chronic passive congestion. In fact, the presence of sheets of these cells in cases of chronic passive congestion, in which swelling might be expected, is in our experience extremely rare. If the separation of these cells from the alveolar walls, furthermore, is in large part caused by the shrinkage of fixation, as Miller's material suggests, these cells even if not swollen should be separable from the alveolar walls as the result of postmortem change in the alveoli of the normal lung. Such, however, is not the case in the human subject. Finally, in the drawing of the highly magnified section of lung from the 35 cm. fetus (fig. 10) remnants of the epithelial lining are still visible. On the right-hand side of the large alveolus can be seen several epithelial cells, joined by a cytoplasmic process, which are in places separated from the alveolar wall in much the same manner as in Miller's illustrations of the pneumonic lung. The separation of the epithelial lining from the alveolar walls is evident throughout this lung, but no epithelial cells are seen in the alveoli of the normal, full term infant (fig. 11). This suggests, first, that epithelial cells are still present and visible in the 35 cm. fetus but are absent in the 48 cm. fetus and, second, that when these cells are present there is no difficulty in seeing

22. Sprunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia: I. Similarity of a Toxin Pneumonia to That Produced by the Viruses, J. Exper. Med. **62**:73 (July) 1935; II. Production of Interstitial Mononuclear Pneumonia by the Bordet-Gengou Bacillus, ibid. **62**:449 (Sept.) 1935. Sprunt, D. H., cited by Macklin, C. C.: Pulmonic Alveolar Epithelium: Report of a Round Table Conference, J. Thoracic Surg. **6**:82 (Oct.) 1936.

23. Cappell, D. F.: Intravitam and Supravital Staining: III. The Nature of the Normal Lining of the Pulmonary Alveoli and the Origin of the Alveolar Phagocytes in the Light of Vital and Supravital Staining, J. Path. & Bact. **32**: 675 (July) 1929.

24. Miller.[5] Footnote 22.

them in sections fixed and stained by ordinary methods. Miller and Sprunt do not seem justified, therefore, in assuming that because such cells are present in the abnormal lung they are also present in the normal lung.

It has been suggested [14] that in the expanded lung the epithelial lining of the alveoli has been stretched so thin as to be invisible. But

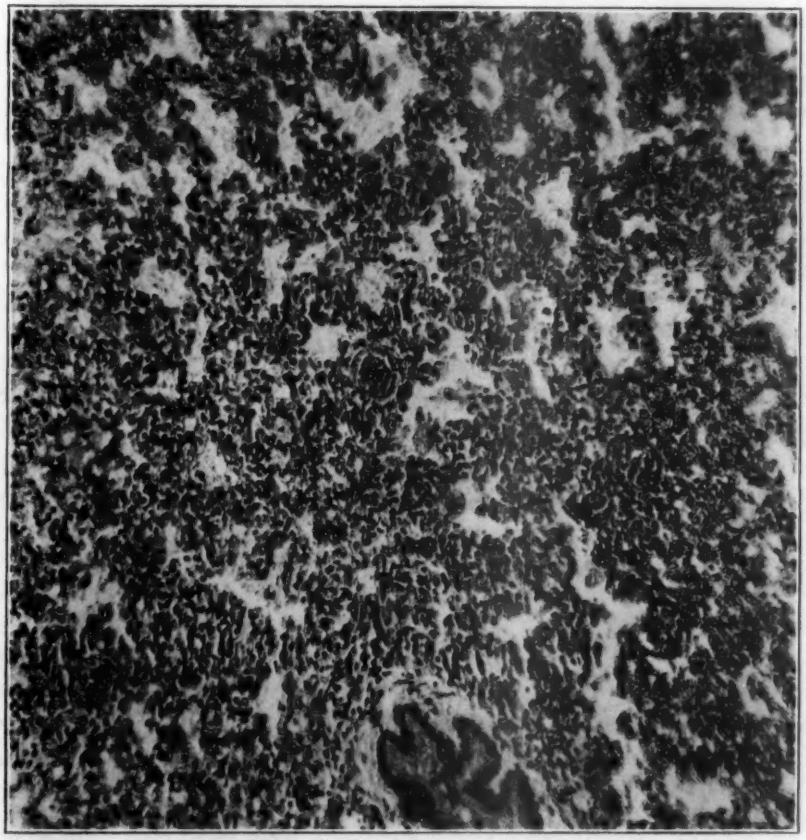


Fig. 12.—Section of the uninjected lung of a 48 cm. fetus. No epithelial cells are visible in the alveolar walls.

if this is true, in the collapsed lung these cells should be so compressed as to be readily demonstrable (Bloom [25]). That no such epithelial lining is visible is evident from the sections of the lungs, injected and uninjected (collapsed), of the same normal 48 cm. fetus (figs. 7 and 12). Not a single epithelial cell can be seen in the collapsed lung, even though the

25. Bloom, W., cited by Macklin, C. C.: Pulmonic Alveolar Epithelium: Report of a Round Table Conference, J. Thoracic Surg. **6**:82 (Oct.) 1936.

alveoli and capillaries are in such close approximation that little space remains for any epithelial cells, visible or invisible.

A small second group of investigators (Palmer,[11b] Wenslaw,[26] Brodersen[27] and Boattini[28]) who admit that the alveoli are not lined by a continuous layer of epithelium have expressed agreement with von Kölliker[29] to the extent of maintaining that only scattered epithelial cells are present among the capillary loops. Von Kölliker also expressed the belief that the capillaries are covered by nonnucleated epithelial "squames" which are derived from these cells. These acellular squames are entirely hypothetic, however, since no one has yet seen them; if they were present in pathologic conditions desquamation would occur and make them visible. It is likely, however, that the isolated cubical or polyhedral cells resembling epithelium which are occasionally seen among the capillary loops of the alveolar walls are in reality reticuloendothelial cells, since they are actively phagocytic (Fried[30]). Probably from such cells originate the large mononuclear phagocytes, the so-called heart failure cells, which are so commonly present in cases of chronic passive congestion and infection.

The third group of investigators comprises those who have expressed the belief that after birth an epithelial lining of the alveoli is not present in the normal lung (Barnard and Day,[12] Clements,[13] Josselyn,[20] Bloom,[25] Fried,[31] Bargmann,[32] Loosli[33] and Gloyne[34]). The inaccuracy of tinctorial methods for the demonstration of epithelium in the normal lung

---

26. Wenslaw, A.: Sur l'ontogenèse de l'épithélium pulmonaire chez l'homme, Compt. rend. Soc. de biol. **104**:611 (June 13) 1930.

27. Brodersen, J.: Ueber die Straub-Körner- und Schaumzellen der Lunge und ihre Funktion, Ztschr. f. mikr.-anat. Forsch. **32**:73, 1933.

28. Boattini, G.: Sulla sifilide pluriviscerale acquisita, Arch. ital. di anat. e istol. pat. **2**:651 (May-June) 1931.

29. von Kölliker, A.: Zur Kenntnis des Baues der Lunge des Menschen, Verhandl. d. phys.-med. Gesellsch. in Würzburg **16**:1, 1881; cited by Palmer.[11a]

30. Fried, B. M., cited by Macklin, C. C.: Pulmonic Alveolar Epithelium: Report of a Round Table Conference, J. Thoracic Surg. **6**:82 (Oct.) 1936.

31. Fried, B. M.: Origin of Histiocytes (Macrophages) in Lungs: Experimental Study by Use of Intratracheal Injections of Vital Stain, Arch. Path. **3**:751 (May) 1927. Fried, B. M., and Whitaker, L. R.: Intratracheal Injection of Iodized Oil: Experimental Studies, Arch. Int. Med. **40**:726 (Nov.) 1927. Fried, B. M.: Allergic Inflammation of the Lungs: Pathogenesis of Lobar Pneumonia, Arch. Path. **18**:865 (Dec.) 1934; Lungs and Macrophage System, ibid. **17**:76 (Jan.) 1934.

32. Bargmann, W.: Zur vergleichenden Histologie der Lungenalveole, Ztschr. f. Zellforsch. u. mikr. Anat. **23**:335, 1935.

33. Loosli, C. G.: The Structure of the Respiratory Portion of the Mammalian Lung with Notes on the Lining of the Frog Lung, Am. J. Anat. **62**:375 (March) 1938.

34. Gloyne, S. R.: The Alveolar Epithelium of the Lung, Brit. J. Tuberc. **32**: 73 (April) 1938.

and the artificial conditions under which epithelial-like cells are seen in the abnormal lung cast doubts on the validity of the evidence that the alveoli are normally lined by epithelium. The absence of demonstrable epithelium in the collapsed lung is also strongly against the existence of an epithelial lining of the alveoli. This group therefore cannot accept the evidence as proving the existence of an *invisible* epithelial lining, especially when it is remembered that of all tissue in the body epithelium is most easily demonstrated by ordinary methods of fixation and staining. Accordingly, the mature alveolar walls must be composed only of a capillary network, with a supporting stroma of connective tissue reticulum, elastica and ground substance.

Although special methods of staining have not been employed because of their doubtful validity, the evidence from this study is against the presence of an epithelial lining of the normal alveoli and therefore supports the belief of this third group that none exists.

The developmental changes of the lung are clinically significant because of the effect of immaturity on respiratory function. The asymmetric subdivision of the respiratory passages probably has no great physiologic importance, but the migration of capillaries at first embedded in mesenchyma to an exposed position in the air sac is most important. Before a body length of 25 to 30 cm. is attained few capillaries are exposed to the potential air spaces and those which are still in the mesenchyma are separated from the air spaces not only by a layer of cuboidal or columnar epithelium but by varying amounts of fetal connective tissue. Prior to the age of 6 lunar months, therefore, respiratory function must be seriously impeded and the chances for independent existence must be slight.

After the age of 6 lunar months, the continued increase in the number of terminal air sacs is accompanied by the exposure of proportionately greater numbers of capillaries to the air spaces and by the presence of progressively fewer epithelial cells which might hinder respiration. At term no visible epithelium remains, and the capillary plexus of the alveolar walls has probably its maximum exposure to the alveolar air.

Whether the mature alveolus at term has an invisible epithelial lining is also of greater academic interest than clinical importance. Since there is no evidence that the hypothetic epithelial lining, if present, disappears during life, the lung at birth has its maximum efficiency so far as its lining goes. But while an epithelial lining is still visible during fetal life, there is every reason to suppose that respirations must be mechanically less efficient than at term. It must be concluded, therefore, that during the fetal period the lung becomes progressively better adapted to respiration, until at term it is most efficient.

The question arose whether the lung might sometimes show a stage of development less mature than that of the body as a whole. Arbitrarily

assuming four stages of development during the period of increase in body length from 20 to 50 cm., we classified the lungs of 493 fetuses obtained at necropsy without knowing the size of the fetus in any case. Our estimation of the stage of development of the fetal lung was found to agree remarkably well with the size of the fetus and the supposed length of gestation. Disproportionate immaturity of the lung, therefore, must be rare and must not usually be an important cause of unexplained respiratory failure in the relatively mature infant.

SUMMARY AND CONCLUSIONS

The development of the fetal lung was studied in 22 infants varying in age from 4 lunar months to full term at the time of birth.

Reconstructions from the injected lungs of fetuses with a body length of 15, 25 and 48 cm., respectively, indicated that subdivision of the respiratory elements is not symmetric or invariably dichotomous and that the number of generations is unequal.

At the 25 to the 30 cm. stage (5 to 6 lunar months' gestation age) protrusion of the mesenchymal capillaries between the epithelial cells of the primitive air sacs takes place, and from then aeration of the pulmonary blood is facilitated by the exposure of the capillaries to the potential air spaces.

After the 25 to 30 cm. stage is attained the epithelium of the terminal air sacs is gradually lost, until at term the mature alveoli normally contain no visible epithelium.

In our opinion the alveoli after birth normally have no epithelial lining.

Before the gestation age of 5 to 6 lunar months the obvious epithelial lining of the terminal air sacs and the position of the mesenchymal capillaries at a distance from the potential air spaces are great impediments to respiration.

The anatomic and clinical significance of these observations is discussed.

EFFECT OF PUBERTAS PRAECOX ON THE AGE AT WHICH ONSET OF WALKING OCCURS

WAYNE DENNIS, PH.D.
UNIVERSITY, VA.

The effect of supernormal size and strength on the age at which the onset of walking occurs has often been discussed, but no factual evidence relative to the question has ever been adduced. In that connection, the cases of most extreme development are probably the most important, since the greater in excess of normal is the bodily development of the child the greater might be expected to be its effect on the age at which walking begins.

The instances of most advanced physical growth in the first and second years of life are undoubtedly those rare cases in which puberty is attained during this period. It has been known since the time of Geoffroy-Saint-Hilaire that premature puberty is preceded and accompanied by an acceleration of skeletal development and of ossification. This is amply shown by the literature on precocious maturity. Smith, in 1822, reported the case of a boy who possessed pigmented pubic hair at 5 months of age and who experienced nocturnal emissions two or three times weekly from 2 years of age onward; he grew with amazing rapidity and when 3½ years old weighed 65 pounds (29.5 Kg.). Durkee's patient, also a boy, grew normally during the first year, but, with the onset of the secondary sex characteristics soon thereafter, he underwent extremely rapid development, weighing 60 pounds (27.2 Kg.) at 4 years of age. Even more precocious was the girl reported on by Morse, who at birth had enlarged breasts and a slight growth of pubic hair and weighed 14 pounds (6.4 Kg.). She reached the menarche at the age of 9 months and when 14½ months old weighed 36 pounds (16.3 Kg.). The girl described by Ambrozic and Baar attained the menarche at 2 years of age. When her skeletal development was assayed roentgenologically at the age of 3 years, she was found to exhibit the ossification which is characteristic of a 12 year old girl. A similar case of premature ossification, studied by modern methods, was reported by Hutchison and Wauhope. The instances cited are characteristic of the cases in which precocious puberty occurred within the first two years of life. In addition, strength is greatly improved, a fact which happens not to be illustrated by the cases cited. The acceleration of development is characteristic of all puberty, normal as well as precocious (Dennis).

Mrs. Wayne Dennis and Mr. M. R. D. Singer aided in collecting the data presented in this paper.

In contrast to the development of the skeletal and muscular systems, the nervous system seems to be affected scarcely at all by pubertas praecox. The surveys of Stone and his collaborators have shown that children who have undergone pubertas praecox are not superior in intelligence, and the longitudinal studies of Gesell and others have disclosed no effect of pubertas praecox on the intelligence quotient. While the evidence concerning the lack of effect of pubertas praecox on the nervous system bears chiefly on intelligence, it may be stated that there has been no difference of opinion about any other effect.

In view of these facts, it is evident that children who have reached puberty at a very early age are far above the age standards in respect to all body measurements. Their bodily proportions resemble those of the adult, their ossification is nearly complete and their strength is greater than that of nonpubescent children of the same height and weight; yet the development of their nervous systems seems unaffected by these changes and is compatible with their chronologic, rather than their physiologic, age. In other words, the cases of such children would provide excellent material for a study of the effect of size and strength on motor development.

With this idea in mind, I have examined the records of cases of pubertas praecox, paying special attention to data on motor development in infancy. The literature on pubertas praecox is extensive; more than 500 cases have been reported. Cases have occurred over many centuries; Pliny referred to a case, as did several other early writers. Their accounts, however, are such that they cannot be used in a scientific survey. The first adequate case studies appeared in the seventeenth century. Reports have steadily increased in number since that time. That reports have been more numerous in modern times seems to be due to greater medical attention and to the increase in population rather than to a real change in the incidence of the condition.

One may say parenthetically that, if the medical literature gives a true picture, the incidence of pubertas praecox does not merely follow the lower end of the distribution curve for normal puberty. Instead of the instances increasing in frequency with age, as would be expected if they were examples of onset of normal puberty at an extremely early age, they decrease. The greatest number of cases occurs during the first year of life. Since the attainment of puberty at the age of 3 or 4 years is sufficiently unusual to warrant attention, it hardly seems possible that the greater frequencies reported at the lowest age levels is a function of the selection of cases for report.

Unfortunately, the majority of case histories give no data relative to behavior. Typically, the reports include physical measurements but no comment on behavioral development. For instance, Keene and Stone and Doe-Kulmann and Stone found that reference to the intelligence of

the subjects with pubertas praecox was made only seldom. The age at which walking began was reported even less often. Although I attempted to examine all the reports of cases contained in the library of the Surgeon General, I have not succeeded in finding any considerable number in which the age at which walking began is stated.

Not all of the records which were examined could be used, since many of the patients who had undergone pubertas praecox had had other abnormal conditions as well. I have included in this study only those cases in which the child exhibiting pubertas praecox was in good health and gave no evidence of any pathologic condition during the first two years of life. This means that cases of precocious puberty associated with tumors of the pineal body and the adrenal glands were excluded. The cases retained were those in which the precocity was of the type usually supposed to result from hypersecretion of the gonads, with no other abnormality. Some cases were excluded because of the presence of rickets and a few because of marked mental retardation, since these conditions are known to affect the onset of walking.

Furthermore, I have included only those cases in which puberty occurred within the first two years of life, since it might have been urged that in cases in which puberty was reached at an age beyond 2 years walking was accomplished before even the earliest phases of pubertal development were begun. The commonly accepted criteria of puberty consist of the appearance of the menarche in the female and the growth of pigmented, kinky pubic hair in the male. Of course these are not isolated phenomena; they are merely the indications of puberty which are the most readily observable and hence the most frequently recorded.

In half of my cases the patient reached puberty during the first year of life. In these instances, without question, the onset of walking did not precede the physiologic development, the effects of which were being considered. In cases in which the patient reached sexual maturity during the second year of life, some of the prepubertal acceleration of growth occurred before the onset of walking.

My data, then, are derived from cases in which puberty was reached during the first two years of life and there was no record of abnormality or any condition known to affect the onset of walking. So far as I know, the patients in my cases differed from unselected children only in the greater maturity of their skeletal systems and their closer approach to adult dimensions and proportions. The sources for the cases, which total 25, are given in the bibliography.

The ages at which walking began range from 9 to 18 months, with an average of 13.58 and a sigma of 2.26. The range is entirely normal, and the average is not distinguishable from that for unselected American children. Nearly all existent norms for the age at which walking began are derived from mothers' reports, as were the ages with which I am

concerned here. Recently the average ages at which walking began were compiled for all the normal groups for which this information has been reported (Dennis and Dennis). The average age for different groups varied from 12.77 to 13.55 months. Since the average reported here falls within 0.03 month of the last-named figure, there is no reason to suppose that the unusual physical development of these children in any way affected the age at which walking began. The correlation coefficient for the age at puberty and the age at onset of walking in my cases was 0.21, with a probable error of 0.135.

Several considerations arise with regard to the composition of my group of 25 cases. Since they are only a small fraction of the total number of cases of pubertas praecox which have been reported, it may be said that they are not representative. In some respects they are not representative cases of pubertas praecox, nor did I wish them to be. In many cases precocious sexual maturity is of pathologic origin. If one wished to find the effect of premature physiologic development per se on walking, it would be foolish to include cases in which other factors obviously exerted influence. The real question of selection has to do with whether my cases are representative of those in which the origin of the precocious development was nonpathologic. Certainly, the authors were likely to note anything unusual, since they were reporting cases of a rare and spectacular disorder. It would not have been surprising if they had noted only those ages at which walking began which were unusually early or unusually late. The fact is, however, that they reported ages which form a normal distribution within the usual range. The reports of extreme ages are rare; the majority fall near the mean. These facts seem to signify that the onset of walking at a very early or a very late age was really unusual in these cases, for the observers could hardly have failed to report such instances had they been frequent. In other words, one must conclude that subjects with pubertas praecox of nonpathologic origin walk, on the average, at the usual age.

It is worthy of note that in many cases it was observed, evidently to the physician's surprise, that the behavioral development of the patient was normal. In many reports other than those listed in the bibliography it is stated that walking and talking and other behavioral activities began at the "normal" time. I could not include these cases, since to do so would have involved the presumption that I understood what the author had in mind as "normal." Nevertheless, these instances furnish added proof that pubertas praecox does not disturb the development of motor skills.

One may ask further whether the patients in these cases may reasonably be compared with present day normal American children. Because of the greater frequency of reports in recent years, 21 of my 25 cases were reported between 1875 and the present, the interval in which

accepted data on normal children have been gathered. In all cases included in the present survey the patient was a member of the white race and was born in the United States, Great Britain, France or Germany. In racial and national origin, therefore, the patients with pubertas praecox are comparable with the members of the normal groups. Approximately half of the children of my group were male and half female, as was the case in the comparative investigations. One must conclude therefore that the evidence is good that the rapid development which precedes and accompanies precocious puberty neither accelerates nor retards the onset of walking.

I do not propose that size, strength and bodily proportions are entirely unrelated to the age at which walking begins. A rational analysis will show that a number of conditions must be fulfilled before it becomes possible for a child to walk. It cannot be doubted that a certain degree of ossification of the bones is essential; it is not conceivable that an infant whose bones are exclusively cartilaginous could walk erect. However, complete ossification is not required, as is shown by the fact that ordinarily this state is not attained until long after the onset of walking. Just what degree of osseous development is needed for walking has not yet been determined.

In addition, it is obvious that some degree of muscular strength is necessary; for this factor also the minimum requirement is still unknown. Furthermore, a certain functional condition of the vestibular apparatus is demanded for the maintenance of balance. Finally, one may mention that the development of certain cortical areas is required, since anencephalous infants, even those who live for several years, are not able to walk. It is, of course, scarcely necessary to add that there are numerous subcortical and peripheral neural structures which are indispensable. It may be that there are still other requirements besides the commonly accepted ones just enumerated. Probably some learning must take place, although the belief is sometimes expressed that walking is an unlearned act. There is also the possibility that certain bodily proportions must be attained before the infant can walk; this was the view of Aristotle, and it is not unfamiliar today. Other suggestions might be made, but those which have been cited are sufficient for the present purpose.

It does not seem likely that all of these conditions are met at the same moment; rather, it is probable that they are met sequentially and that walking will occur only when the last requirement is fulfilled.

If this analysis is correct, the age at which several of these factors are completed may be advanced considerably without any effect on the age at which walking begins so long as the final requirement is fulfilled at the usual time. It is only the final factor which directly affects the onset of erect locomotion.

What is the final requirement the achievement of which immediately precedes the onset of walking? It is not known as yet. But apparently it is not the attainment of a certain height, weight, strength or set of bodily proportions, since even when these are achieved prematurely walking occurs at the usual time. It is likely that the final factor in normal development is a neural one, but evidence pointing to this conclusion has been adduced only by a process of elimination.

While premature growth does not mean premature locomotion, the reverse of this statement may not be true. Retardation of growth probably will retard walking, since walking cannot occur until all of the necessary phases of development have been completed.

SUMMARY

The reports of cases of pubertas praecox have been examined to obtain information relative to the age at which healthy infants who attained puberty within the first two years of life began to walk. Data were obtained for 25 cases. The range of ages at which walking began in these cases was from 9 to 18 months, with a mean of 13.58. These figures are substantially the same as those for children of normal growth.

Since pubertas praecox is associated with extraordinary bodily changes in the direction of adult size, proportions and ossification and since the age at which patients with pubertas praecox begin to walk is normal, it must be concluded that none of these developments is the final factor the attainment of which marks the onset of walking. It is not denied that certain requirements as to size, strength and ossification are necessary for walking, but it appears that these are present some time before walking ordinarily begins and do not initiate its onset. However, if development in these three phases were retarded, it is probable that walking also would be delayed.

BIBLIOGRAPHY

Ambrozic, M., and Baar, H.: Ein Fall von Makrogenitosomia praecox und Nebennierentumor bei einen Jährigen Mädchen, Ztschr. f. Kinderh. **27**:135-142, 1920.

Bennett, C. L.: Pubertas Praecox in a Girl of Four, Endocrinology **16**:529-532, 1932.

Dennis, W.: The Adolescent, in Carmichael, L.: Handbook of Child Psychology, to be published.

——and Dennis, M. G.: The Effect of Cradling Practices upon the Onset of Walking in Hopi Children, J. Genet. Psychol. **56**:77-86, 1940.

Doe-Kulmann, L., and Stone, C. P.: Notes on the Mental Development of Children Exhibiting the Somatic Signs of Puberty Praecox, J. Abnorm. & Soc. Psychol. **22**:291-324, 1927.

Durkee, S.: Precocity in a Boy, Boston M. & S. J. **23**:299-301, 1841.

Elterich, T. O.: Analysis of the Syndrome of Precocious Menstruation, Pennsylvania M. J. **34**:629-635, 1931.

Friedel, E.: Ueber den frühreifen Knaben Albert Stromeyer, Verhandl. d. berl. Gesellsch. f. Anthrop., 1877, pp. 443-448.

Geoffroy-Saint-Hilaire, I.: Histoire générale et particulière des anomalies de l'organisation chez l'homme et les animaux, Paris, J. B. Baillière, 1832-1837, vols. 1-3.

Gesell, A.; Thoms, H.; Hartman, F. B., and Thompson, H.: Mental and Physical Growth in Pubertas Praecox: Report of Fifteen Years' Study of a Case, Arch. Neurol. & Psychiat. **41**:755-772 (April) 1939.

Hutchison, R., and Wauhope, G.: A Case of Precocious Puberty, Brit. J. Child. Dis. **21**:57-61, 1924.

Keatinge, G. F.: Two Cases of Precocious Puberty, J. Obst. & Gynaec. Brit. Emp. **33**:653-656, 1926.

Keene, C. M., and Stone, C. P.: Mental Status as Related to Puberty Praecox, Psychol. Bull. **34**:123-133, 1937.

Klein: Ein Fall von Pubertas praecox, Deutsche med. Wchnschr. **25**:47, 1899.

Lenz, J.: Vorzeitige Menstruation, Geschlechtreife und Entwicklung, Arch. f. Gynäk. **99**:67-144, 1913.

Morse, J. L.: Precocious Maturity, Arch. Pediat. **14**:241-250, 1897.

A Case of Abnormal Physical and Sexual Development in an Infant of Two Years, Probably Due to a Tumor of the Pineal Gland, ibid. **30**:179-191, 1913.

Obmann, K.: Ueber vorzeitige Geschlechtsentwicklung, Deutsche med. Wchnschr. **42**:195-198, 1916.

Orel, H.: Kleine Beiträge zur Vorerbungswissenschaft, Ztschr. f. Konstitutionslehre **13**:691-698, 1928.

Pryor, W. R.: A Case of Precocious Development, Am. J. Obst. **20**:245-251, 1887.

Rowe, A. W., and Lawrence, C. H.: Studies of the Endocrine Glands: IV. The Male and Female Gonads, Endocrinology **12**:591-662, 1928.

Rudel, E.: Beitrag zur Pathologie der Menstruatio praecox, Würzburg, Bonitas-Bauer, 1889, p. 21.

Siegel, A. E.: Influence of the Adrenals and Ovaries upon Precocious Secondary Sexual Development, Arch. Pediat. **41**:265-272, 1924.

Smith, J. G.: Some Account of a Boy in Whom the Generative Organs Have Been Prematurely Developed, London M. Reposit. **17**:353-358, 1822.

Tierney, J. L.: Pubertas Praecox, M. Clin. North America **6**:31-60, 1922.

von Lenhossék: Geschichte einer ungewöhnlich schnellen Entwickelung bei einem Mädchen, nach einem amtlichen Berichte mitgetheilt und durch physiologisch-pathologische Bemerkungen erläutert, Med. Jahrb. d. k. k. oesterr. Staates **6**: 68-125, 1820.

Wachs, O.: Ein Fall von vorzeitiger Menstruation bei einem dreijährigen Kinde, Ztschr. f. Geburtsh. u. Gynäk. **1**:173-188, 1877.

Wheelan, H.: Precocious Menstruation: Observations on Two Cases of Pubertas Praecox, Endocrinology **9**:353-371, 1925.

White, A.: Historical Account of Philip Haworth, a Boy in Whom Signs of Puberty Commenced at an Early Age, Med.-Chir. Tr., London **1**:276-288, 1809-1811.

Ziehen: Fall von Gigantismus, Berl. klin. Wchnschr. **43** (pt. 2):1198-1199, 1906.

HYPERBILIRUBINEMIA IN THE NEWBORN

LEONARD T. DAVIDSON, M.D.

KATHARINE K. MERRITT, M.D.

AND

A. ASHLEY WEECH, M.D.

NEW YORK

Physiologic hyperbilirubinemia during the early postnatal period has been observed by many investigators. The stimulus and justification for still another study of the phenomenon have come from improvements in methods. A simple photoelectric technic for the analysis of small samples has made it possible for the first time to record the changes in the level of bilirubin in the serum by means of daily observations on a large number of infants. In the present study such measurements were started on the first day of life after the level of bilirubin in serum from the umbilical cord had been determined. At the time of each analysis the presence or absence of clinical icterus in the infant was recorded. The data have been examined for interrelations among such factors as the concentration of bilirubin in the cord serum, the maximum intensity of the process, the age at the time the maximum level was attained, the duration of elevated levels and the presence of clinical jaundice. Ranges of normal variability have been charted for each day of the postnatal period. On the basis of the studies a significant association has emerged between the level of bilirubin in the cord serum and both the duration and the intensity of hyperbilirubinemia in the infant. The bearing of these observations on the causation of neonatal jaundice is discussed.

REVIEW OF THE LITERATURE

Previous publications dealing with the descriptive and the etiologic aspects of physiologic jaundice are numerous. Only those papers which bear directly on the results of the present investigation are referred to here.

In 1913 Ylppö [1] published the results of extensive investigations into the behavior of bile pigment in the blood, the stools and the urine

From the Sloane Hospital for Women, the Babies Hospital and the Departments of Obstetrics and Gynecology and of Pediatrics of Columbia University College of Physicians and Surgeons.

1. Ylppö, A.: Icterus neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeboren, Ztschr. f. Kinderh. **9**:208 (Dec.) 1913.

of the fetus and the newborn infant. In numerous instances the amount of bilirubin in the blood was measured more than once during the neonatal period; for each of 12 infants from five to eight determinations were made, beginning with the analysis of a specimen of cord blood and continuing with examinations of samples of blood obtained throughout the neonatal period. On a few of these infants further observations

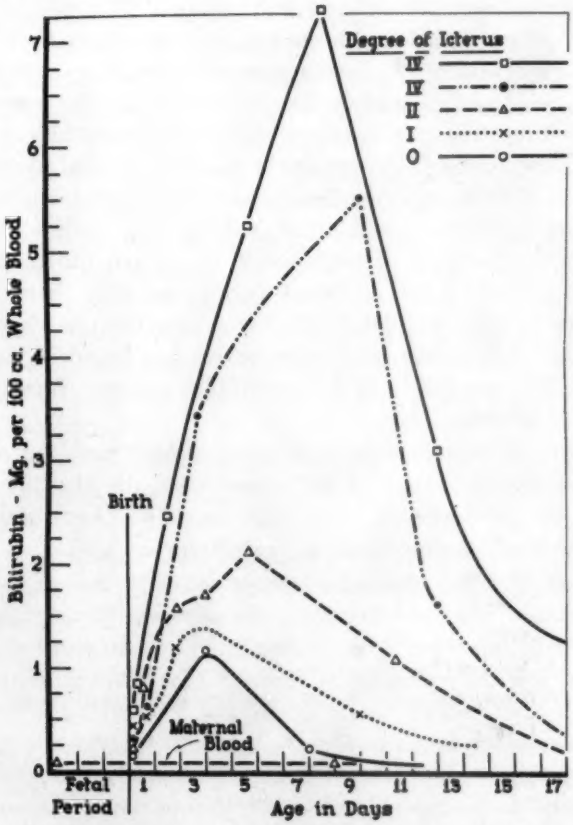


Chart 1.—Levels of bilirubin in the blood of 5 newborn infants (from Ylppö [1]).

were made up to the eighth week of life. A chart constructed from these data, which because of its historical importance is reproduced here (chart 1), shows the variations in the levels of bilirubin of 5 infants selected because they had different degrees of hyperbilirubinemia. Ylppö concluded that the level of bilirubin is always above normal in cord blood, that the level in the infant's blood continues to rise for three to ten days and then declines, that clinical icterus is manifest whenever the concentration rises above a critical level of 1.25 mg. of bilirubin per hundred cubic centimeters of blood and that the degree of icterus and

the level of bilirubin in the blood parallel each other closely. He also observed that high levels in the cord blood were more apt to be followed by jaundice in the infant than the lower levels. Infants in whom the bilirubin reached a peak level by the third day did not exhibit jaundice. It is important to note that Ylppö's analyses were made on whole blood; these values cannot be compared directly with those of others who have worked with serum or with plasma.

Hirsch,[2] almost simultaneously with Ylppö in 1913, reported observations on 180 infants which established a relation between the level of bilirubin in the cord serum and subsequent jaundice in the infant. Infants who remained completely free of icterus had an average level of 0.86 mg. of bilirubin per hundred cubic centimeters of cord serum, and infants who exhibited unmistakable jaundice had an average level of 1.4 mg. of bilirubin per hundred cubic centimeters of cord serum. For 12 infants from two to four serial analyses were made to determine the variations in the level of bilirubin in the serum during the early days of life. A rapid rise occurred during the first three days; in icteric infants the level remained high for a longer time, while in non-icteric infants it fell rapidly to a value below that found at birth. The critical level for jaundice was 5 mg. of bilirubin per hundred cubic centimeters of serum.

Subsequent investigators have in general confirmed the results of Ylppö and of Hirsch. Lack of agreement as to the absolute quantity of bilirubin in the serum is apparently explained by differences in analytic procedure; most reports are consistent regarding the changes in the levels of bilirubin which characterize the early days of life. Lucas and his associates [3] observed that the curve obtained by averaging levels for a number of infants reaches a maximum on the third day; when the values are low the maximum is reached somewhat earlier, and when they are high it is reached later. Schiff and Faerber [4] confirmed most of Ylppö's results but failed to observe any relation between the intensity of jaundice and the degree of hyperbilirubinemia. Goldbloom and Gottlieb [5] found an increased level of bilirubin in the cord serum and in the peripheral blood serum of all the infants they examined. Values above 2 mg. (4 van den Bergh units) per hundred cubic centimeters

2. Hirsch, A.: Die physiologische Ikterusbereitschaft des Neugeborenen, Ztschr. f. Kinderh. **9**:196 (Dec.) 1913.

3. Lucas, W. P.; Dearing, F. D.; Hoobler, H. R.; Cox, A.; Jones, M. R., and Smyth, F. S.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.

4. Schiff, E., and Faerber, E.: Beitrag zur Lehre des Ikterusneonatorum, Jahrb. f. Kinderh. **97**:245 (March) 1922.

5. Goldbloom, A., and Gottlieb, R.: Icterus Neonatorum, Am. J. Dis. Child. **38**:57 (July) 1929.

of serum were always associated with clinical jaundice. When jaundice developed the levels were still higher at the end of ten days than at birth. Heiniö [6] made frequent (for the first five days, daily) observations on 9 infants and noted the usual early rise and subsequent decline in the level of serum bilirubin. Of interest are his observations in a case in which the level of bilirubin was higher than normal (1.8 mg. per hundred cubic centimeters of serum) on the first day but sank gradually to normal without showing any rise. There was no icterus. Snelling [7] used the icteric index in making daily observations on the variations in the level of bilirubin in the serum of 20 newborn infants. His results agree with those of other investigators. The results of similar studies with the icteric index have been reported by Gordon and Kemelhor [8] and by Bonar.[9] Ross and his co-workers [10] examined the serum of 63 infants on the fourth or fifth day of life, using the van den Bergh technic. Twenty-two jaundiced infants had an average level of 5 mg. (10 units) of bilirubin per hundred cubic centimeters of serum, and for 41 nonjaundiced infants the average level was 2.2 mg. (4.4 van den Bergh units). Waugh and his associates,[11] making 250 determinations according to the method of Malloy and Evelyn,[12] demonstrated that hyperbilirubinemia was present at birth and increased during the first four days of life and that the level of bilirubin then fell toward normal. In general, clinical icterus was observed when the bilirubin reached a level of 5 mg. or more per hundred cubic centimeters of blood.

MATERIAL FOR STUDY

The 132 infants studied were born in Sloane Hospital. They are divided into four groups: (1) 30 infants for whom a sample of cord blood was obtained and on whom daily observations were continued for eleven or twelve days after birth; (2) 63 infants for whom a sample of cord blood was obtained but on whom the subsequent daily observations were terminated when the level of bilirubin in the

6. Heiniö, P.: Ueber das gegenseitige Verhalten des Blutbilirubins und der Erythrozyten sowie des Hämoglobins bei Icterus neonatorum, Acta pædiat. **14**:474, 1933.

7. Snelling, C. E.: Icterus Neonatorum, J. Pediat. **2**:399 (April) 1933.

8. Gordon, M. B., and Kemelhor, M. C.: Icterus Neonatorum, J. Pediat. **2**:685 (June) 1933.

9. Bonar, B.: The Icterus Index in the New-Born Infant, Am. J. Dis. Child. **50**:1143 (Nov.) 1935.

10. Ross, S. G.; Waugh, T. R., and Malloy, H. T.: The Metabolism and Excretion of Bile Pigment in Icterus Neonatorum, J. Pediat. **11**:397 (Sept.) 1937.

11. Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn: II. Direct and Total Blood Bilirubin; Determinations Over a Nine-Day Period, with Special Reference to Icterus Neonatorum, Am. J. M. Sc. **199**:9 (Jan.) 1940.

12. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

blood commenced to decrease; (3) 12 infants for whom a sample of cord blood was not obtained but on whom daily observations regarding serum bilirubin were made, and (4) 27 infants on whom observations were begun when clinical icterus appeared. The infants in the first three groups were selected entirely at random, so that the applicability of the results of the observations to the population of the clinic could be estimated. A certain number of infants from the entire group were examined at approximately weekly intervals after discharge until the serum bilirubin reached a stable, and presumably normal, level.

The group studied represented a cross section of a mixed metropolitan population, but the infants were chiefly from the underprivileged classes. Approximately 90 per cent of them were of the "white" race, and the remaining 10 per cent were "colored." Since the term "colored" is applied to both African and West Indian Negroes, many of whom have an admixture of white blood, it was sometimes impossible to determine the predominant racial strain.

METHODS

Clinical observations on the presence or absence of icterus of the mucous membranes, scleras and skin were made daily. The difficulties of making consistently accurate appraisals of jaundice because of racial differences, variations in the amount of light available and changes in weather conditions have been stressed by several observers. Examinations by means of a daylight bulb were discontinued because the results were less accurate than those obtained with ordinary daylight, even under varying weather conditions. We applied a tongue depressor with considerable force to the mucous membrane of the lower jaw and also to the skin of the forehead or the chin. This procedure often made visible icterus which was not otherwise apparent. On the basis of the several observations the degree of icterus was assessed.

The cord blood was collected by cutting the cord on the maternal side of the clamp and allowing the blood to flow into a sterile 15 cc. centrifuge tube. The time after birth when the cord was cut varied somewhat in different cases but averaged about five minutes. No attempt was made to clamp the cord immediately, as was done in the studies carried out by Book.[13] A 10 cc. sample of cord blood was usually collected. The tube was put in an ice box, where the sample was protected from both artificial and solar light. By centrifugation this amount of blood yielded approximately 3 cc. of serum. Blood from the infant was obtained by puncture of the heel, the usual amount collected being 0.5 cc., from which an average of 0.1 to 0.15 cc. of serum was secured. The collection was facilitated by soaking the infant's heel in a pan of warm water; hanging the foot over the edge of the table also aided the blood to drip freely. Occasionally, pressure around the ankle and foot, or rubbing the incision with dry gauze, was necessary to maintain the flow of blood. It was more difficult to obtain the blood soon after birth than on subsequent days. In general, capillary blood was taken for the first time from the infant's heel during the first twenty-four hours after birth. Often it was taken a few hours after birth, and in a few instances it was not obtained until more than twenty-four hours after birth.

The method for measuring the bilirubin in the serum was adapted from the procedure of Ernst and Förster,[14] which utilizes acetone to precipitate the serum protein and yield a clear, supernatant fluid in which the intensity of the yellow

13. Book, N.: Icterus Neonatorum, Canad. M. A. J. **33**:269 (Sept.) 1935.

14. Ernst, Z., and Förster, J.: Ueber die Bestimmung des Blutbilirubins, Klin. Wchnschr. **3**:2386 (Dec.) 1924.

color of bilirubin can be estimated. The estimation of color intensity was made by means of a photoelectric photometer especially designed to accommodate the 50 mm. optical cells of the Zeiss-Pulfrich *Stufenphotometer*. The capacity of these cells is about 1 cc. The readings were made in blue light obtained by a filter of the following composition: Corning no. 511 violet glass, of 3 mm. thickness; Jena optical filter glass GG-5, of 2 mm. thickness, and Corning light shade aklo glass 396, of 2 mm. thickness. Solutions of bilirubin exhibit maximum light absorption at a wavelength of 440 millimicrons; the filter described transmits light with a wavelength of 410 to 490 millimicrons, with a peak transmission at a wavelength of 450 millimicrons. With this filter in our instrument, solutions of bilirubin have shown only slight deviation from the Beer-Lambert law.

The chief objection in the past to use of the yellow color of serum as a measure of bilirubin concentration has been that lipochromes, such as carotene, which are also yellow, interfere with the determination. In evolving the method which we have used, this objection could have been overcome by applying the van den Bergh reaction to the acetone extract of serum. Diazotization was not adopted both because results can be reproduced with greater accuracy when the additional manipulations are not carried out and because we did not find that the serum of newborn infants contains significant amounts of lipochromes. Fourteen consecutive samples of serum from newborn infants were treated with purified petroleum benzine to establish this point. The extract was then placed in the photometer, and its light absorption was measured with the same blue filter as was used in determining the concentration of bilirubin. In no instance was there a visible yellow tint to the extract; the amount of lipochrome, calculated as bilirubin from the photometer readings, was usually less than 0.05 mg. per hundred cubic centimeters, and in only 1 sample did it reach a level of 0.10 mg. per hundred cubic centimeters. Such values are within the range of error in measuring bilirubin and are wholly insignificant in appraising the general course of physiologic hyperbilirubinemia.

The analytic procedure was carried out as follows: Five-tenths cubic centimeter of distilled water was pipeted into a 15 cc. centrifuge tube. Serum was drawn to the mark in a capillary pipet calibrated to contain 0.1 cc. and delivered, with several rinsings, into the water in the centrifuge tube. Two cubic centimeters of acetone was added, and thorough mixing was effected with a stirring rod, which was subsequently withdrawn. The tube was then placed in the ice box for fifteen minutes, or until well chilled. Throughout these and later manipulations every effort was made to minimize exposure to light. We have routinely stored samples and tubes in a covered can, removing them only in subdued light to carry out essential steps in the procedure. Centrifugation of the chilled tubes was carried out for fifteen minutes in 300 cc. bronze cups, which were filled with cracked ice before the tubes were inserted. Immediately afterward the supernatant fluid was transferred to another tube, which was stoppered and allowed to come to room temperature. The purpose of chilling during this phase of the procedure was to obtain a solution free from any trace of turbidity. When chilling is neglected the fluid becomes warm while in the centrifuge, and even if it is clear when first removed, slight cloudiness may develop as its temperature falls.

By carrying out simultaneous analyses of 23 samples of serum from newborn infants according to the method described and according to the macrophotoelectric procedure of Malloy and Evelyn,[12] the photometer readings were calibrated. The latter method is in routine use in this laboratory; results obtained with it have been calibrated repeatedly by determinations on known dilutions of pure bilirubin solution,[15] and it has also been used in another part of our work with newborn infants

15. The bilirubin used was manufactured by Hoffmann-LaRoche, Inc.

in which data about the directly and the indirectly reacting fractions of bilirubin were wanted. Results of the two methods were compared because both methods are used in this laboratory. The outcome of the comparison is presented graphically in chart 2. There can be no doubt that the measurement of bilirubin in diverse types of serums has been simplified and improved by the procedure of Malloy and Evelyn. At the same time, observations in this laboratory indicate the need for further refinements before confidence can be placed in the absolute values yielded by any method. Addition of hemoglobin (laked red cells) to icteric serum has always decreased the intensity of color in the van den Bergh reaction; such addition has not affected the yellow color obtained in an acetone extract. Such considerations undoubtedly account for the lack of perfect agreement in the data of chart 2.

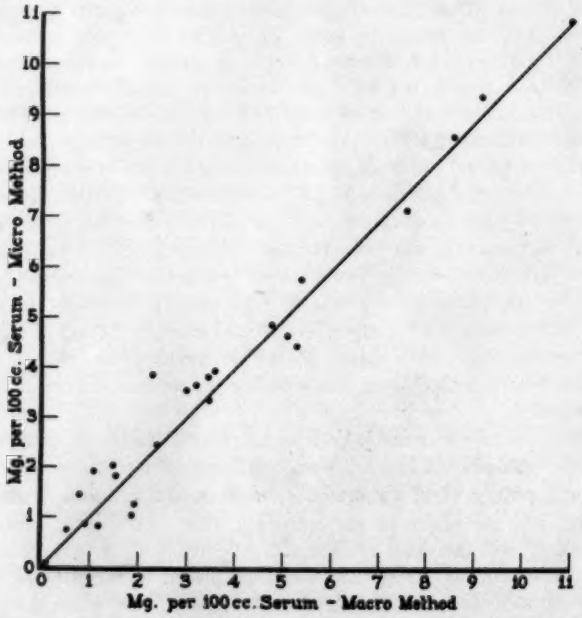


Chart 2.—Results of determinations of bilirubin levels by a micromethod and a macromethod.

Finally, it should be noted that the procedure employing the acetone extract is not applicable to serums which exhibit a direct reaction to the van den Bergh test. Infants who have a physiologic jaundice do not have serum of this type. When directly reacting bilirubin is present, it appears to be precipitated quantitatively with the protein by acetone. Under these circumstances the precipitate will have a yellow color, and that the result will be unreliable can be recognized at once.

RESULTS

The nature of the data to be presented and analyzed will be clarified by chart 3, in which are presented the serial observations on a single infant during the first thirteen days of life. The rapidity of change

during this period, a circumstance which justifies the frequent measurements, should be stressed. The appearance, development and decline of clinical icterus are indicated at the bottom of the chart. Three degrees of jaundice, moderate, marked and severe, through which this infant successively passed, were recorded. In this case, as in the cases of all individual icteric infants, the degree of icterus paralleled the level of serum bilirubin. This point is important in view of the variability exhibited among different infants. Finally, the absence of a time lag in the disappearance of jaundice after the decline of the bilirubin curve below the level at which icterus developed should be noted. Some such lag might reasonably be expected, since diffusion of bilirubin from the skin

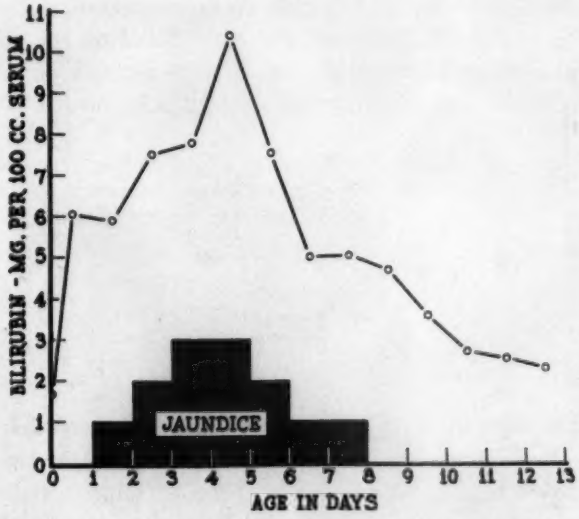


Chart 3.—Bilirubin levels and intensity of jaundice in an infant during the first thirteen days of life.

into the circulation must follow a lowering of concentration in the serum. However, the data for this infant and for the others suggest that adjustments between the skin and the blood stream take place rapidly and that such diffusion of the bilirubin is not manifest when observations are made at twenty-four hour intervals.

A total of 99 infants were examined daily from birth for the presence of jaundice. The difficulty of assessing this symptom when the degree of icterus is slight has already been mentioned. It is apparent that on the number of infants affected all observers will not agree. Icterus was recorded as present on at least one occasion in 63 infants of our group, that is, in approximately two thirds of the subjects. In 10 of these it was observed only once and then was characterized as mild. If the 10 are excluded on the grounds that the diagnosis of jaundice was questionable,

there remain 53 infants, slightly more than half of the group, for whom two or more observations established the diagnosis with reasonable certainty. The distribution of the 63 infants with respect to the intensity and the duration of jaundice is recorded in table 1. Thirty-seven infants, or 59 per cent, had moderate icterus; in 20 infants, or 32 per cent, the icterus was marked, and in 6 infants, or 9 per cent, it was severe. The duration of icterus is recorded roughly in days; the figures correspond to the number of daily observations at which the symptom was noted. A few inaccuracies have been unavoidable because the infants left the hospital and escaped observation. The duration in these instances is recorded as the number of days the symptom had persisted at the time of the last examination. Thus, 1 infant with marked jaundice left the hospital on the fourth day of duration of the symptom, and 1 infant with moderate jaundice departed on the fifth and 2 on the sixth day. Table 1 indicates that the symptom was present for at least a week in 25 infants, or 40 per cent of the group. Icterus is known to have lasted

TABLE 1.—*Duration and Intensity of Jaundice in Sixty-Three Newborn Infants*

Degree of Icterus	Duration of Icterus in Days (Inclusive)				Total
	1	2–3	4–6	7+	
Moderate	10	10	13	4	37
Marked	0	1	4	15	20
Severe	0	0	0	6	6
Total	10	11	17	25	63

longer than ten days in 10 of 21 of these infants who continued under observation. In 2 infants it was noted as still present on the twenty-first and the twenty-fifth day, respectively. Finally, table 1 indicates, as might be expected, a high degree of correlation between the degree of jaundice and its persistence.

The ages of the 63 infants at the onset of observable jaundice are shown in the frequency diagram (chart 4). In 25 per cent the symptom was noted during the first twenty-four hours, in 45 per cent during the second day and in 22 per cent during the third day. In only 2 cases did the symptom appear after the fourth day and in none after the sixth day. In interpreting the data for the 16 infants who showed jaundice during the first twenty-four hours, it should be remembered that some infants were observed when they were only a few hours old and others when nearly twenty-four hours had elapsed since birth. Undoubtedly, therefore, the hour of birth was a factor in determining whether jaundice was observed on the first or the second day of life. A more detailed analysis cannot be attempted, since observations were made only once each day.

In studying the figures for the concentration of serum bilirubin for the entire group of randomly selected infants, we have been impressed by the fact that on no single day of life are the values for individual infants distributed symmetrically about their averages. On the contrary, one finds that the majority of infants exhibit levels which are less than the average; the data for a few infants in whom extremely high levels were reached affect the average unduly. Histograms constructed from such data always show a distribution which is skewed toward the higher values. This skewness will be noted in several of the charts. It is evident even in the values for bilirubin in cord serum when the levels are

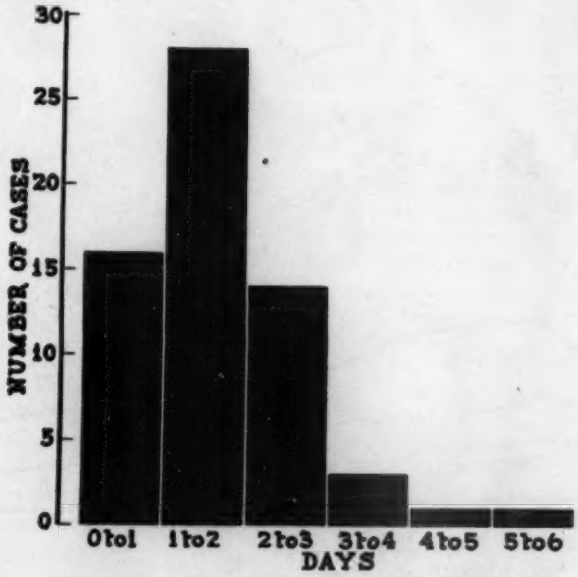


Chart 4.—Age at onset of jaundice.

relatively low and becomes more pronounced as the concentrations rise toward their maximums. The point is stressed because previous investigators have expressed their results in the form of average curves and because it is clear that such curves give an erroneous impression of the usual course of events. To avoid this error we have computed medians rather than averages as the measure of central tendency. The median of a series of values marks the point above which and below which exactly 50 per cent of the values will be found. In order to describe the distribution about the median, we have likewise calculated first and third quartiles and first and ninth deciles. Below the first quartile and above the third quartile will be 25 per cent of the values; that is, 50 per cent will lie between the two quartiles. Below the first decile and above the ninth decile will be 10 per cent of the values; that is, 80 per cent will fall between the two deciles.

The results of these calculations are utilized to show in chart 5 the changes in the level of bilirubin in the serum during the first ten days of life. The curves begin with the values for bilirubin in cord serum, which are shown at age zero on the chart. It will be recalled that cord serum was not obtained in all cases and that on some infants observations were continued only until the level of bilirubin in the serum was noted to be declining. Consequently, the number of observations on each day of the neonatal period was not constant. The actual number of observations available for each computation is indicated at the bottom of the chart.

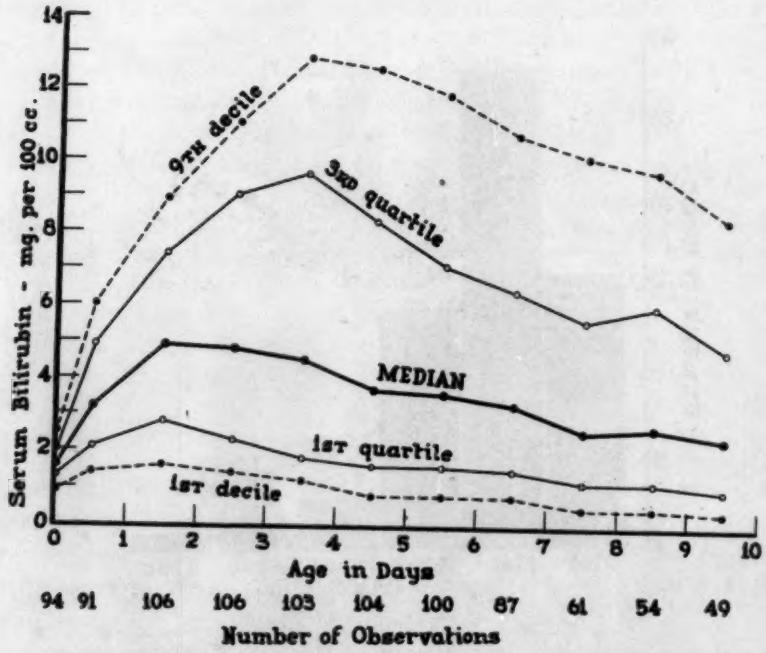


Chart 5.—Variations in bilirubin levels during the first ten days of life. Levels in cord serum are shown at age 0 days.

The curves disclose the interesting fact that whereas the first decile, the first quartile and the median all reach their peak levels on the second day of life, the third quartile and the ninth decile attain their peaks on the fourth day. This means that in general the more intense the hyperbilirubinemia, the older the infant will be when the process begins to subside. The curves also provide standards for appraising the relative incidence of individual values on each day of the neonatal period; such appraisal can be of value in assessing the significance of values. For the purpose of defining normal ranges, additional interest attaches to the maximum levels recorded on each day of the neonatal period. These were: first day, 15.6 mg. per hundred cubic centimeters; second day,

21.3 mg.; third day, 26.2 mg.; fourth day, 25.5 mg.; fifth day, 22.0 mg.; sixth day, 19.7 mg.; seventh day, 18.6 mg.; eighth day, 17.8 mg.; ninth day, 15.3 mg., and tenth day, 14.5 mg. These maximum values were for 2 infants; the figures for the first five days were for 1 infant, and those for the sixth to tenth days, inclusive, were for the other. Neither of them exhibited signs at the time or during their subsequent course which could be interpreted as evidence of a pathologic type of icterus. In agreement with the results of other observers, our studies disclose no exception to the general rule that bilirubin in the infant's serum always rises to a level above that in serum from the umbilical cord. In fact, the level on the first day of life was always higher than that in the

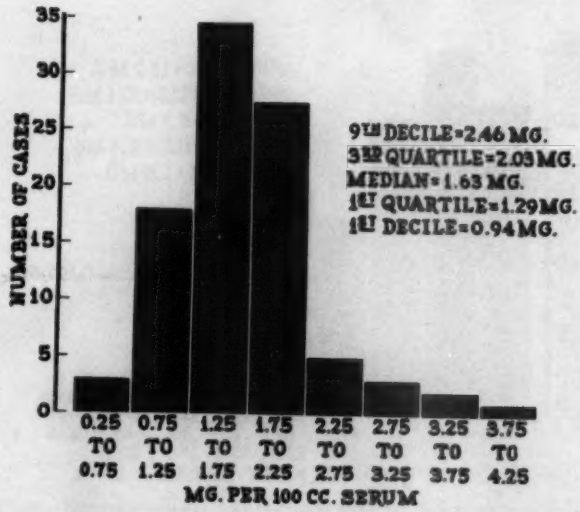


Chart 6.—Level of bilirubin in cord serum.

cord serum, and for 18 infants on whom two observations were made during the first twenty-four hours, the second value obtained was, with 1 exception, higher than the first.

The distribution of the bilirubin values for the 94 randomly selected samples of cord serum is shown separately in chart 6. The average value for these samples, 1.69 mg. of bilirubin per hundred cubic centimeters of serum, is only slightly higher than the median level of 1.63 mg. The degree of asymmetry or skewness is therefore slight; the modal concentration is approximately 1.52 mg. per hundred cubic centimeters. The lowest value for cord serum was 0.42 mg. per hundred cubic centimeters; there were 7 infants in whom the level was less than 1.0 mg., and in 2 of them the subsequent concentration of bilirubin in the serum never exceeded 1.0 mg. The highest value for bilirubin in the cord serum included in this analysis was 3.9 mg. per hundred cubic centi-

meters. We have encountered 1 other normal infant, not included in the randomly selected group, for whom the value for bilirubin in the cord serum was 4.1 mg. per hundred cubic centimeters. Such values appear to be comparable with those for cord serum from infants with erythroblastosis foetalis and serve to warn that high levels of bilirubin cannot in themselves be considered indicative of a pathologic process.

The distribution of 106 randomly selected infants with respect to the maximum level of bilirubin in the serum, regardless of the day on which it was reached, is shown in chart 7. In this group are 12 infants not included in the group used for the foregoing analysis because for them no sample of cord blood was available. The distribution of the values is markedly asymmetric. The average maximum level of 6.73

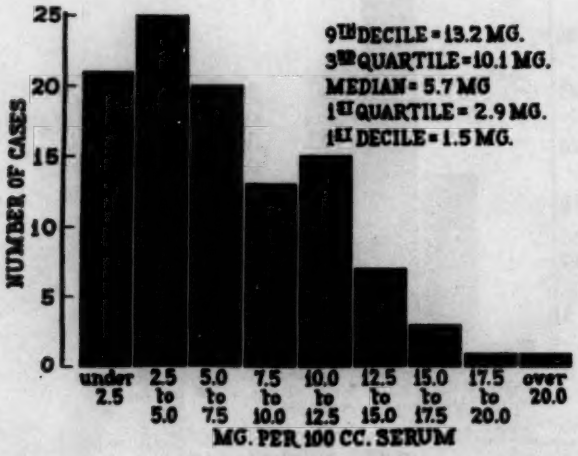


Chart 7.—Maximum level of bilirubin in the serum for 106 infants selected at random.

mg. of bilirubin per hundred cubic centimeters of serum is well above the median of 5.68 mg. Calculation of the approximate value for the mode yields the figure of 3.58 mg. of bilirubin per hundred cubic centimeters of serum as the level most likely to be reached during this phase of life. We have already mentioned the 2 infants whose maximum levels of bilirubin in the blood did not exceed 1.0 mg. per hundred cubic centimeters. The lower of the peak values for these 2 infants was 0.86 mg. A maximum level of bilirubin in excess of 20 mg. per hundred cubic centimeters of blood was observed only once in this series of infants; we have noted a similarly high level in 1 other infant. The age at which the peak levels were reached varied considerably: during the first day, 13 infants; on the second day, 38 infants; on the third day, 21 infants; on the fourth day, 18 infants; on the fifth day, 11 infants; on the sixth day, 4 infants, and on the seventh day, 1 infant. In all the

subjects the level of bilirubin had commenced to decline by the end of the first week. We have already noted in connection with the discussion of chart 4 that a high degree of correlation exists between the height of the bilirubin curve and the age at which the maximum level of bilirubin is attained.

An attempt was made to determine for many of these infants the age at which the concentration of bilirubin subsides to a constant, and presumably normal, value. Because of difficulties in carrying out regular follow-up examinations, it has not been possible to continue to an older age curves of the type presented in chart 4. Only a few general

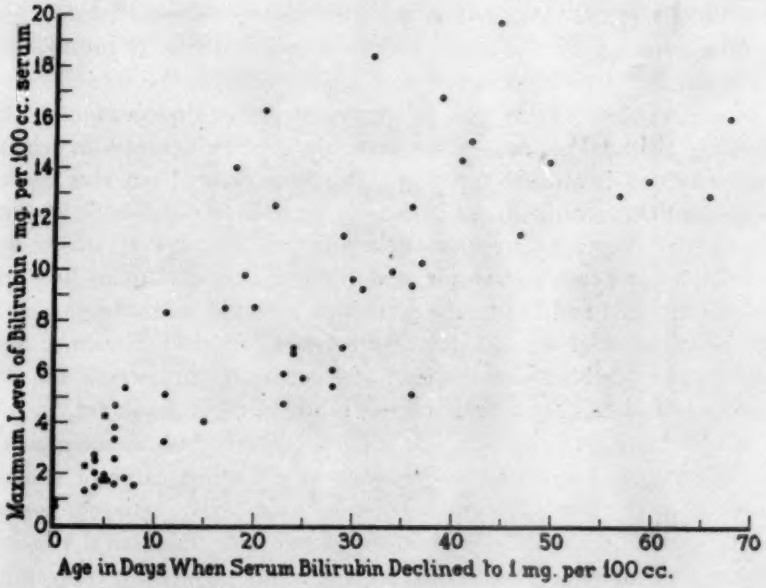


Chart 8.—Age at which the level of serum bilirubin declined to 1 mg. per hundred cubic centimeters.

statements can be made. On 21 infants serial observations were continued at intervals of one or occasionally two weeks until it appeared that no further decline was going to take place. At this stage the average level of bilirubin was 0.50 mg. per hundred cubic centimeters of serum, with a standard deviation of 0.13 mg. Chart 4 indicates that subsidence of the concentration of bilirubin to this level takes place in a small number of infants during the first ten days of life. The infants selected for prolonged follow-up study did not attain stabilized levels until after the first month and in a few cases not until more than two months had elapsed. Some idea of the persistence of neonatal hyperbilirubinemia

can be obtained from chart 8, which shows for 57 infants the age at which the concentration of bilirubin declined to 1 mg. per hundred cubic centimeters. The values are charted in relation to the maximum level of bilirubin attained. A rough correlation can be seen between the height of the maximum level of bilirubin in the blood and the persistence of hyperbilirubinemia.

The preceding paragraphs have been concerned mainly with description. Observations on approximately 100 infants have been utilized to present the incidence, the age at onset, the duration and the intensity of clinical physiologic icterus. Determinations of bilirubin in serum have been analyzed to portray the path of the bilirubin curve during the first ten days of life, the variations in the path among different infants and the time required for the curve to flatten and stabilize at presumably normal values. It is legitimate now to inquire whether the several items of description are interrelated or represent rather independent components of the total picture. That some law of order operates in regard to these factors is already apparent. We have pointed out that correlations exist between the intensity and the duration of physiologic icterus, between the degree of hyperbilirubinemia and the age at which the condition commences to subside and between the maximum level of bilirubin attained and the total duration of elevated serum levels. We shall now comment on the relation between hyperbilirubinemia and clinical icterus and between the level of bilirubin in cord serum and the subsequent variations in bilirubin levels in the blood of the infant.

Since staining of the skin, the scleras and the mucous membranes with bilirubin and its oxidation products is the direct cause of clinical jaundice, it is clear that an association must exist between hyperbilirubinemia and icterus. Most investigators have observed a relation between the two symptoms, although there is little agreement concerning the degree of hyperbilirubinemia which separates the jaundiced infant from the nonjaundiced, and in one investigation [4] no relation was discovered. The reason for the variation in the results obtained by different authors is at least partly clarified by the results of this investigation. We have already stated that judging from the serum bilirubin curves of individual infants, there is a close parallelism between the height of the bilirubin levels and the appearance and fading of jaundice. Among the curves of different infants, however, there is wide variability. Some infants become jaundiced with relatively low levels of serum bilirubin, and some have exceedingly high levels without exhibiting staining of the superficial tissues. Baby M., a member of the white race, exemplified the latter statement. For him serial determinations of the concentration of bilirubin per hundred cubic centimeters of serum yielded the follow-

ing values: cord serum, 1.51 mg.; first day, 4.7 mg.; second day, 7.0 mg.; third day, 9.7 mg.; fourth day, 10.3 mg.; fifth day, 12.1 mg., and sixth day, 11.4 mg. Jaundice was not observed at any of the daily examinations.

To elucidate the overall relation between bilirubin levels and jaundice, we have utilized data for all patients for whom we had the results of concomitant clinical examinations and chemical analyses. A total of 1,215 observations on 120 infants were available. Because the incidence of severe jaundice is low, both second and third degrees were classified as "marked," and first degree jaundice was classified as moderate. Since preliminary analysis failed to disclose any difference between the data for white and those for colored infants, no racial distinction was made. The results are summarized in chart 9. Although the association between jaundice and the degree of hyperbilirubinemia is well shown, it is clear

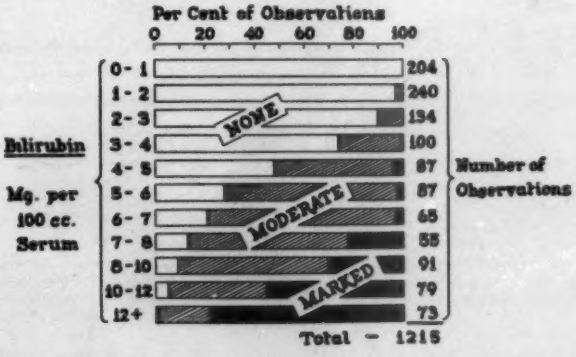


Chart 9.—Relation between the level of serum bilirubin and jaundice.

that a critical level of serum bilirubin, above which icterus is present and below which it is absent, does not exist. With a concentration of 4 to 5 mg. of bilirubin per hundred cubic centimeters of serum, clinical observations revealed associated jaundice in slightly more than half (52 per cent) of the infants; a clear majority of infants with concentrations of bilirubin above this level were icteric, and only a minority of those whose serum bilirubin was below this level exhibited the symptom. Our experience with cases of hemolytic disease in older children is relatively small. No doubt with them, too, a zone rather than a level separates those who do from those who do not exhibit jaundice. Nevertheless, we believe that most of these children will show the symptom if their concentration of bilirubin is in the neighborhood of 2 mg. per hundred cubic centimeters of serum. If this is true, it follows that newborn infants are relatively resistant to the development of jaundice, but why

is not apparent. The capillaries of the infant are certainly no less permeable to bilirubin than those of the older child. It is possible, of course, that the answer lies in some peculiarity of the integument of the young infant which makes it less able to bind the pigment.

As we stated earlier, both Ylppö and Hirsch noted a relation between the quantity of bilirubin in the serum from the umbilical cord and the subsequent variations of bilirubin levels in the infant's blood. Later investigators, apparently, have not been much interested in the possible significance of this association. The volume of data assembled in the present study is ideally suited for studying this association. The data for 95 infants are presented in the form of a contingency table (table 2), which is the simplest way in which the association can be demonstrated. In preparing the table the infants were divided into four groups according to whether the level of bilirubin in the cord serum was above or below the median level for cord serum and the maximum value for

TABLE 2.—*Relation* of Bilirubin Concentration in Cord Serum and Maximum Level of Serum Bilirubin*

Mg. of Bilirubin per 100 Cc. of Cord Serum	Maximum Level of Bilirubin, Mg. per 100 Cc. of Serum		Total
	Under 5.3	Over 5.3	
Under 1.64	40	7	47
Over 1.64	8	40	48
Total	48	47	95

* Chi square = 44.5; value required for significance (P = 0.01): 6.6.

the level of serum bilirubin was above or below the median value. It will be observed that of the 47 infants for whom the value for bilirubin in the cord serum was relatively low, 40, or 85 per cent, also exhibited relatively low levels of serum bilirubin subsequently and only 7, or 15 per cent, exhibited subsequent high levels. In contrast, of the 48 infants for whom the value for bilirubin in the cord serum was relatively high, only 8, or 17 per cent, showed subsequent low levels of serum bilirubin and 40, or 83 per cent, subsequent high levels. These data are impressive; the value of chi square computed from the contingency table indicates overwhelming significance. Direct correlation of the two sets of data, the levels of bilirubin in the cord serum and in the infant's serum, yields a figure for r, the correlation coefficient, of 0.71. Since the standard error of r is only 0.05, this result likewise indicates a highly significant degree of association. There can be no doubt, then, that a direct relation exists between the level of bilirubin in serum from the umbilical cord and the subsequent height of the bilirubin levels in the infant's serum.

Since an association has already been pointed out between the intensity and the duration of hyperbilirubinemia in the infant, a relation might be expected a priori between the level of bilirubin in the cord serum and the duration of hyperbilirubinemia in the infant. The proof that such an association does exist is furnished in table 3, in which the duration of hyperbilirubinemia in the infant is measured in terms of the time required for the bilirubin to rise to its maximum level. The data were again divided at the median with respect to the concentration of bilirubin in the cord serum. The value of 16 for chi square is indicative of a highly significant degree of association. The conclusion of the preceding paragraph can therefore be extended to the statement that a direct relation exists between the level of bilirubin in serum from the umbilical cord and both the intensity and the duration of hyperbilirubinemia in the infant.

TABLE 3.—*Relation* of Level of Bilirubin in the Cord Serum and Duration of Rising Levels of Bilirubin in the Blood of the Infant*

Mg. of Bilirubin per 100 cc. of Cord Serum	Duration† of Rising Levels of Bilirubin		Total
	Less Than 48 Hours	More Than 48 Hours	
Less than 1.64	32	15	47
More than 1.64	13	35	48
Total	45	50	95

* Chi square = 16.0; value required for significance (P = 0.01): 6.6.
† By "duration of rising levels of bilirubin" is meant the time elapsed between birth and the attainment of the maximum level of bilirubin in the blood.

COMMENT

The demonstrated fact of a high degree of correlation between the level of bilirubin in serum from the umbilical cord and the subsequent levels of serum bilirubin in the infant almost forces the conclusion that the course of bilirubin levels in the infant's blood is already determined at the time of birth. It hardly seems possible that the process responsible for the demonstrated association can operate effectively and consistently in the brief but variable period which elapses between birth and the severing of the cord. The excessive destruction of erythrocytes which characterizes the neonatal period appears to be caused by release from fetal anoxemia. The adjustment follows the moment of birth. Since bilirubin is formed from destroyed hemoglobin, it is possible that variations in the rate of disintegration of red cells could modify the course of neonatal icterus. Such modification must, however, be slight and not the chief cause of the abnormal bilirubin levels, or the association noted by Ylppö and Hirsch and demonstrated by our work could not exist. In fact, recent investigators [16] have failed to find a significant correlation

16. Ross, Waugh and Malloy.[10] Waugh, Merchant and Maughan.[11]

between the rate of destruction of red cells and the intensity of physiologic hyperbilirubinemia.

There remain two other circumstances which require reconciliation. The work of previous investigators appears to have established a relation between certain aspects of placental metabolism and the phenomenon of icterus in the infant. Schick [17] pointed out that the fetal placenta at one stage of intrauterine life plays an important part in metabolizing maternal hemoglobin so that later the needs of the maturing fetus can be supplied; the singular susceptibility of premature infants to physiologic icterus was explained by the theory that they are born when placental metabolism of this type is active. Wagner [18] supported the theory by showing that the placentas of premature infants contain more iron than those of full term infants. Williamson [19] analyzed the placentas of infants who were subsequently observed with respect to icterus; he reported a definite association between the amount of placental iron and the intensity of jaundice. Finally, Gottlieb and Kearns,[20] who reported the results of histologic studies of degenerative change in the placenta, found a clear correlation between the degree of change and the intensity of icterus in the infant. Important as these observations are, they have failed to receive adequate recognition because it is difficult to see in them an explanation for the increasing hyperbilirubinemia of the early days of life. As a result attention has been given to another feature, namely, the status of hepatic function, with respect to the bilirubin-excreting power of the liver, in the young infant. Many authors have expressed the belief that the liver of the newborn infant is functionally immature and that the phenomenon of icterus is related to individual variations in the degree of functional maturity. Snelling [7] has described histologic characteristics of the livers of newborn infants. Ross and his associates [10] reported that there is a lower excretion of bile pigment during the first week of life by jaundiced infants than by those who are not jaundiced. In fact, there is reason to believe [9] that the degree of hyperbilirubinemia which often ensues could not develop on the basis of excessive hemolysis alone.

Before attempting to bring together the facts just cited, it is pertinent to ascertain whether functional immaturity of the liver, operating before

17. Schick, B.: Der Icterus neonatorum eine Folge des Abbaues mütterlichen Blutes, Ztschr. f. Kinderh. **27**:231 (Jan.) 1921.

18. Wagner, R.: Icterus neonatorum und Eisengehalt der Placenta, Ztschr. f. Kinderh. **27**:251 (Jan.) 1921.

19. Williamson, A. C.: Placental Iron and Its Relationship to Icterus Neonatorum, Surg., Gynec. & Obst. **37**:57 (July) 1923.

20. Gottlieb, R., and Kearns, P. J.: Icterus Neonatorum: IV. The Rôle of the Placenta in Visible Icterus Neonatorum, J. Clin. Investigation **10**:319 (June) 1931.

birth, can be a factor in determining some of the results. Ylppö pointed out that the first meconium, presumably the meconium formed before birth, contains little bile pigment; the average value for samples from 6 full term infants was 33 mg. per hundred cubic centimeters. These results indicated to him that only a small amount of bilirubin is formed before birth. It is important, however, to note that even this amount of bile pigment if retained in the circulation instead of being excreted into the bowel would produce significant concentration in the plasma. Even if the plasma volume of the fetal circulation is estimated liberally at 300 cc., a concentration of over 10 mg. of bilirubin per hundred cubic centimeters would be attained from this cause alone. If variations in the rate of excretion into the bowel affect the level of bilirubin in the fetal plasma, one would expect an inverse relation between the concentration of bile pigment in the first meconium and the bilirubin concentration both in the cord serum and in the infant's serum. Ylppö's data, given in

TABLE 4.—*Results of Ylppö's Analyses of First Meconium* of Eight Infants*

Degree of Icterus	Mg. of Bilirubin per 100 Cc. of First Meconium	
	Individual Values	Average
None	63.4; 38.1	50.8
First	21.9	21.9
Second	23.7; 24.6	24.2
Third	25.5	25.5
Fourth	3.9; 3.9	3.9

* Ylppö termed the material "fetal meconium."

table 4, suggest that such a relation may indeed exist. The first meconium of 2 infants in whom no visible icterus developed contained an average of 50.8 mg. of bile pigment per hundred cubic centimeters; for 4 infants in whom first, second and third degrees of jaundice developed, the average content was 23.9 mg. Finally, the meconium of 2 premature infants in whom extreme icterus (fourth degree) developed had a content of only 3.9 mg. of bilirubin per hundred cubic centimeters. The data of Ross and his associates [10] are in harmony with these results, though the differences are less striking. For 21 infants without jaundice the meconium of the first day averaged 48.2 mg. of bile pigment per hundred cubic centimeters; for 14 infants with jaundice the first meconium averaged 34.8 mg. The difference between the values for icteric and nonicteric infants is perhaps not so large as one might expect, but since the groups were divided on the basis of clinical icterus rather than of the degree of hyperbilirubinemia, they may be significant. The data at least render plausible the theory that functional immaturity of the liver, operating before birth, has an effect on the concentration of bilirubin in the cord serum.

We have evolved a concept of the genesis of icterus neonatorum which takes cognizance of the foregoing facts. In the course of fetal development there comes a time when the expanding organism must draw heavily on maternal sources for the material from which to synthesize its tissues. For a part of the function of synthesis the fetus is already sufficient; for other parts it is not. Observations [21] begun by Claude Bernard and continued by others have demonstrated that the liver of the young fetus is unable to form and store glycogen. At this stage of development glycogenesis is a function of the placenta. It has been found that as development proceeds the placenta contains less and less glycogen while the fetus, particularly the fetal liver, contains more and more. An analogous situation may be imagined for the processes which provide the fetus with substance for building blood. Maternal hemoglobin must be broken down into elements which can cross the barrier to the fetal side of the placenta. These elements must then be delivered to the fetus in a form suited to the degree of functional maturity which has been achieved. Whatever chemical transitions may be involved, it is clear that either little bilirubin is formed or that if it is formed a mechanism exists, probably in the placenta, which permits its effective utilization for the building of new hemoglobin. The available evidence does not indicate that bilirubin can cross the placenta, either to or from the fetus. At this stage of development the placenta contains large stores of iron, as was shown by Wagner. Probably the stores are in a passive state, awaiting the process of functional ripening in the fetus. In any case they serve as an inverse measure of the degree to which function has matured. We may think of a relation between the integrity of the entire placenta and the rate at which function in the fetus is able to develop. The presence of excessive degenerative change appears to be associated with relative immaturity of the liver; at least, such change predisposes to icterus in the infant.[20]

Just before birth, then, a stage has been reached in the development of fetal function and in the transfer of function from the placenta to the fetus which exhibits considerable individual variation. When development is less complete the placenta still contains appreciable amounts of iron and has undergone more than the usual amount of degenerative change; because the function of the fetal liver is relatively underdeveloped, the small amounts of bilirubin liberated at this stage tend to remain in the circulation and not to enter the bowel. At the time of birth the status is revealed by the relatively high concentration of bilirubin in the cord serum. Then follows the first respiration, with

21. Needham, J.: Chemical Embryology, London, Cambridge University Press, 1931, vol. 2. The work of Claude Bernard and of subsequent investigators is discussed critically in this volume.

release from fetal anoxemia, the breakdown of hemoglobin to meet the conditions of a new environment and the consequent formation of large quantities of bilirubin. For the time being excretion of the pigment is relatively inefficient, and the phenomenon of icterus ensues. As the destruction of excess hemoglobin slows and as hepatic function develops rapidly under the conditions of increased oxygen supply, the level of bilirubin in the plasma begins to fall and the icterus begins to fade. However, if the hyperbilirubinemia has been severe, the achievement of mature function, with a return of the bilirubin to a low, stabilized level, may not be achieved for one or more months.

By means of the theory which we have outlined, the degree of physiologic hyperbilirubinemia can be related to the physiologic maturity of the infant at the time of birth. To a certain extent the degree of maturity affects the infant as a whole. In the present stage of knowledge it is not possible to be dogmatic regarding specific functions, and the power of the liver to excrete bilirubin must be thought of as a single function the development of which is paralleled by that of other functions. Available evidence indicates the existence of five barometers which can be used to measure the degree of functional maturity. These are (1) the iron content of the placenta, (2) the histologic structure of the placenta, (3) the amount of bilirubin in the cord serum, (4) the amount of bilirubin in the first meconium and (5) the subsequent levels of serum bilirubin in the infant.

SUMMARY

A rapid microanalytic procedure for determining levels of bilirubin in serum has been utilized to obtain daily, serial observations on 132 infants during the neonatal period. For 63 infants the observations commenced with analyses of serum from the umbilical cord. Concomitant records were made of the presence or absence of clinical icterus.

On the basis of the clinical observations, the incidence, the age at onset, the duration and the intensity of neonatal icterus have been discussed. The values for bilirubin in serum have been analyzed to indicate the variations in the bilirubin level during the first ten days of life, the individual differences in regard to bilirubin levels and the time required for the bilirubin to reach and to maintain a presumably normal level.

Positive correlations were found between the intensity and the duration of physiologic icterus, between the degree of hyperbilirubinemia and the age at which the process attains its maximum intensity and between the maximum height of the bilirubin level and the total duration of elevated levels of bilirubin in the serum.

For individual infants there was a close parallelism betwen the level of bilirubin in the serum and the appearance, intensity and fading of

jaundice. There was pronounced variability among the individual curves; so a broad zone of values rather than a critical level of serum bilirubin may be considered to separate the icteric from the nonicteric infants. Clinical observations revealed that at a concentration of 4 to 5 mg. of bilirubin per hundred cubic centimeters of serum, approximately half of the infants had jaundice; a clear majority of those infants whose level of bilirubin was above this figure were icteric; only a minority of the infants with a concentration of bilirubin below this level exhibited icterus.

Highly significant associations were found between the level of bilirubin in serum from the umbilical cord and both the intensity and the duration of hyperbilirubinemia in the infant.

The data are discussed in the light of pertinent results by previous investigators, and a rational theory of the genesis of neonatal hyperbilirubinemia is outlined. In terms of the theory the degree of hyperbilirubinemia is a measure of the functional maturity of the infant at the time of birth.

PHOSPHORUS RETENTION IN CHILDREN WITH CHRONIC RENAL INSUFFICIENCY

THE EFFECT OF DIET AND OF THE INGESTION OF ALUMINUM HYDROXIDE

SMITH FREEMAN, M.D.
AND
WILLIE MAE CLIFTON FREEMAN, M.D.
CHICAGO

Advanced renal insufficiency is accompanied by an elevation of the inorganic phosphorus content of the blood and frequently by a decrease in the concentration of serum calcium.[1] These alterations may be of importance in precipitating or aggravating certain symptoms which frequently accompany renal insufficiency.[2] No satisfactory regimen has been described for reducing the concentration of phosphorus in the blood to a minimum. Nor is it apparent from the literature whether the phosphorus intake in the diet or its absorption is of importance in influencing the inorganic phosphorus content of the serum of persons with renal insufficiency.

There is experimental evidence to indicate that it is possible, by the selection of a diet low in phosphorus, to reduce the inorganic phosphorus content of the serum of normal animals, as well as to reduce the excretion of phosphorus in the urine.[3] It has also been shown that in human beings and in dogs the absorption of inorganic phosphorus from the intestine can be impaired by the ingestion of aluminum

---

From the Department of Physiology and Pharmacology, Northwestern University Medical School, and the Children's Memorial Hospital.

A part of the material contained in this paper was included in an exhibit in the Section on Pediatrics at the Ninety-First Annual Session of the American Medical Association, New York, June 11 to 16, 1940.

1. Myers, V. C.; Schmitz, H. W., and Rohdenburg, E. L.: Inorganic Phosphorus and Calcium of Blood in Nephritis, Arch. Int. Med. **37**:233 (Feb.) 1926.

2. (*a*) Harrison, T. R., and Mason, M. F.: Medicine **16**:1, 1937. (*b*) Binger, C. A. L.: J. Pharmacol. & Exper. Therap. **10**:105, 1917. (*c*) de Wesselow, O. L. V.: Lancet **2**:163, 1923. (*d*) Mitchell, A. G., and Guest, G. M.: J. Pediat. **3**:192, 1933. (*e*) Drake, J. G.; Albright, F., and Castleman, B.: J. Clin. Investigation **26**:203, 1937.

3. Schneider, H. A., and Steenbock, H.: J. Biol. Chem. **128**:159, 1939. Freeman, S.: Unpublished data.

hydroxide.[4] By combining the feeding of a low phosphorus diet with the ingestion of aluminum hydroxide it should be possible to reduce the absorption of phosphorus to a minimum.

The present study, carried out on children with chronic renal insufficiency, was undertaken to determine whether or not the measures mentioned, singly or in combination, will significantly improve the health and alter the concentration of inorganic phosphorus in the serum and the urine of such patients. An attempt was made to correlate the chemical changes in the blood and urine with the clinical and roentgenologic manifestations of the disease. Observations on a child with normal kidneys are included for the sake of comparison and as an indication of the extent to which it is possible to affect the blood and urine by such procedures.

METHODS

The metabolic studies were carried out while the children were in the Children's Memorial Hospital. When not confined to the hospital, the patients were seen regularly in the outpatient department. Their diets were prepared by a dietitian who had received special instructions concerning the precautions one must observe in preparing a diet low in phosphorus. A three day interval for adjustment to a change in diet or to the addition or withdrawal of medicaments was allowed prior to the collection of urine for any given period. Blood for analysis was usually drawn on the day before the end of a period. Specimens of urine collected over a three or five day period were combined; concentrated hydrochloric acid was used as a preservative.

The inorganic phosphorus contents of the serum and the urine were determined by the Kuttner-Lichtenstein method as modified by Bodansky.[5] The calcium content of the serum was estimated by the method of Clark and Collip.[6] The concentration of nonprotein nitrogen was determined by the micro-Kjeldhal method.[7]

Aluminum hydroxide and calcium lactate were customarily fed during or just before a meal. Calcium lactate was administered as a 5 per cent solution in fruit juices. In some instances the administration of aluminum hydroxide was in numerous small doses throughout the day.

The technic used for preparing the low phosphorus diet is similar to that reported on previously and is not materially different from that described by Bauer and Aub.[8] A simple alteration was to omit dairy products, with the exception of butter, from the diet. If a more rigid restriction of the phosphorus intake is desirable, a diet providing 0.2 to 0.3 Gm. of phosphorus a day can be constructed by using egg white, gelatin and the white meat of fowl as the sources of protein. Such a diet will allow a child 1 Gm. of protein per pound (454 Gm.)

---

4. Fauley, G. B.; Freeman, S.; Ivy, A. C.; Atkinson, A. J., and Wigodsky, H. S.: Aluminum Phosphate in the Therapy of Peptic Ulcer: Effect of Aluminum Hydroxide on Phosphate Absorption, Arch. Int. Med. **67**:563 (March) 1941.

5. Bodansky, A.: J. Biol. Chem. **99**:197, 1932.

6. Clark, E. P., and Collip, J. B.: J. Biol. Chem. **63**:461, 1925.

7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 527.

8. Bauer, W., and Aub, J. C.: J. Am. Dietet. A. **3**:106, 1927.

of body weight per day and will provide an adult with half that much. A sample diet for a child weighing 30 pounds (13.6 Kg.) is given in table 1. Analysis showed that the amount of the low phosphorus diet typically consumed in a day by a child weighing 35 pounds (15.9 Kg.) contained 0.2 Gm. of phosphorus. In reducing the phosphorus content of the diet its calcium content is also lowered; for this reason it is desirable to add calcium to the diet in the form of the lactate or the gluconate. The amount of calcium which should be added probably depends somewhat on the level of the serum calcium. As was pointed out by Park and Eliot,[9] it is difficult to restrict the intake of phosphorus without reducing the nutritive value of the diet. One may partially overcome this difficulty by providing

TABLE 1.—*Low Phosphorus Diet for One Day*

	Total Intake,* Gm.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calcium, Gm.	Phosphorus, Gm.
Breakfast						
Orange juice	120	0	0	16	0.034	0.0190
Farnia (dry)	16	1.7	0	12	0.008	0.0200
Bread, white	30	3.0	0	15	0.008	0.028
Butter, washed	15	0	12.7	0	0	0
Sugar	10	0	0	10	0	0
Lunch						
Bacon	15	1.5	9.7	0	0.0009	0.0054
Riced potato	60	1.3	0	11	0.0084	0.0348
Sliced tomato	100	1.0	0	3	0.0060	0.0150
Bread, white	15	3.0	0	15	0.0080	0.0280
Butter, washed	15	0	12.7	0	0	0
Banana	70	2.1	0	14	0.0063	0.0217
3 p. m. Grape juice	100	0.4	0.2	18.5	0.0110	0.0110
Supper						
Egg white	111	9.0	0	0	0.0120	0.0120
Rice, polished	75	2.0	0	18.0	0.0020	0.0140
Asparagus, fresh	60	0.6	0	1.8	0.0150	0.0230
Bread, white	30	3.0	0	15.0	0.0080	0.0280
Butter, washed	15	0.0	12.7	0	0	0
Peach, fresh	100	0.5	0	12.0	0.0160	0.0240
Total	957	29.1	48.0	161.3	0.1386	0.2839

* Quantities given are for a child weighing 30 pounds (13.6 Kg.) and provide a total of 1,193 calories. Apples, melons, pumpkin, pears and berries without seeds in jellies could be substituted for the fruit listed; squash, sweet potato, celery, onion, egg plant, carrots and cabbage could replace the vegetables listed, and the white meat of fowl and gelatin could serve as sources of protein in place of those given.

specific sources of the vitamin B complex and of vitamins A and D. It is difficult to find a source of the B vitamin complex that does not contain considerable quantities of phosphorus, but a supplement of several members of the B complex can be provided by certain liver fractions, such as the one employed in this study. This liver extract,[10] which has a low phosphorus content, was used as a dietary supplement when a patient was fed the low phosphorus diet for any extended period. Since liver extracts are relatively low in thiamine it is necessary to add this vitamin also (0.75 mg. of thiamine hydrochloride daily was the amount used in the present study). Cod liver oil can be used as a source of vitamins A and D although this oil contains phosphorus; for this reason it may be preferable to use

9. Park, E. A., and Eliot, M. M., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 3, chap. 29, p. 18.

10. The liver extract used, known as fraction E, was manufactured by the Wilson Laboratories.

viosterol in oil and carotene in oil as the sources of vitamin D and A, respectively, or some fish oil concentrate, such as percomorph liver oil. The intake of vitamin D should be liberal, and perhaps large doses may be of value in certain instances.

CLINICAL DATA

CASE 1.—R. M. S., a 10 year old white girl, was admitted to the hospital complaining of blurred vision and pain in the muscles of both calves. She was known to have had albuminuria since she was 2 years of age, and during the past eight years there had been occasional periods of drowsiness, nausea and vomiting, with these symptoms becoming more pronounced during the past three

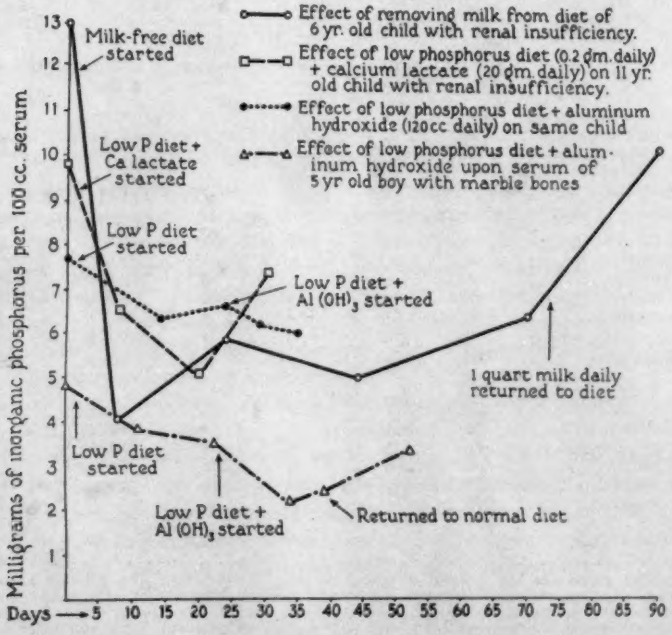

Effect of removing milk from diet of 6 yr. old child with renal insufficiency.
Effect of low phosphorus diet (0.2 gm. daily) + calcium lactate (20 gm. daily) on 11 yr. old child with renal insufficiency.
Effect of low phosphorus diet + aluminum hydroxide (120 cc daily) on same child
Effect of low phosphorus diet + aluminum hydroxide upon serum of 5 yr old boy with marble bones
Milk-free diet started
Low P diet + Ca lactate started
Low P diet started
Low P diet + Al (OH)3 started
1 quart milk daily returned to diet
Low P diet started
Low P diet + Al (OH)3 started
Returned to normal diet
Milligrams of inorganic phosphorus per 100 cc. serum
Days
13
12
11
10
9
8
7
6
5
4
3
2
1
5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90

Fig. 1.—The effect of diet on the inorganic phosphorus content of the serum of 2 children with renal insufficiency and 1 child with osteopetrosis, who had normal kidneys. The solid line indicates values for the patient in case 2; the broken line and the dotted line, values for the patient in case 1, and the line of dots and dashes, values for the child with normal kidneys.

years. Examination revealed pallor, generalized purpura, some puffiness beneath the eyes and a blood pressure of 142 mm. of mercury systolic and 96 mm. diastolic. Examination of the urine revealed marked albuminuria and a low specific gravity (1.010 to 1.014). The hemoglobin content of the blood was 70 per cent (Sahli), and there were 3,440,000 red cells and 6,700 white cells per cubic millimeter; the differential and platelet counts were normal. Chemical examination of the blood gave the following results: nonprotein nitrogen, 69 mg. per hundred cubic centimeters; serum calcium, 10.9 mg.; serum inorganic phosphorus 7.7 mg., and cholesterol, 170 mg. The ascorbic acid content of the blood was 0.92 mg. per hundred cubic centimeters. Intravenous pyelograms failed to visualize the kidneys, and retrograde pyelograms revealed structures compatible with a diagnosis of

infantile kidneys. After this diagnosis was made the child went home, where she remained for six weeks, with persistence of the complaints which had brought her to the hospital. At the end of this time she was readmitted for a more thorough study of her calcium and phosphorous metabolism. At this time the nonprotein nitrogen content of the blood was 133 mg. per hundred cubic centimeters, and the values for the calcium and inorganic phosphorus of the serum were

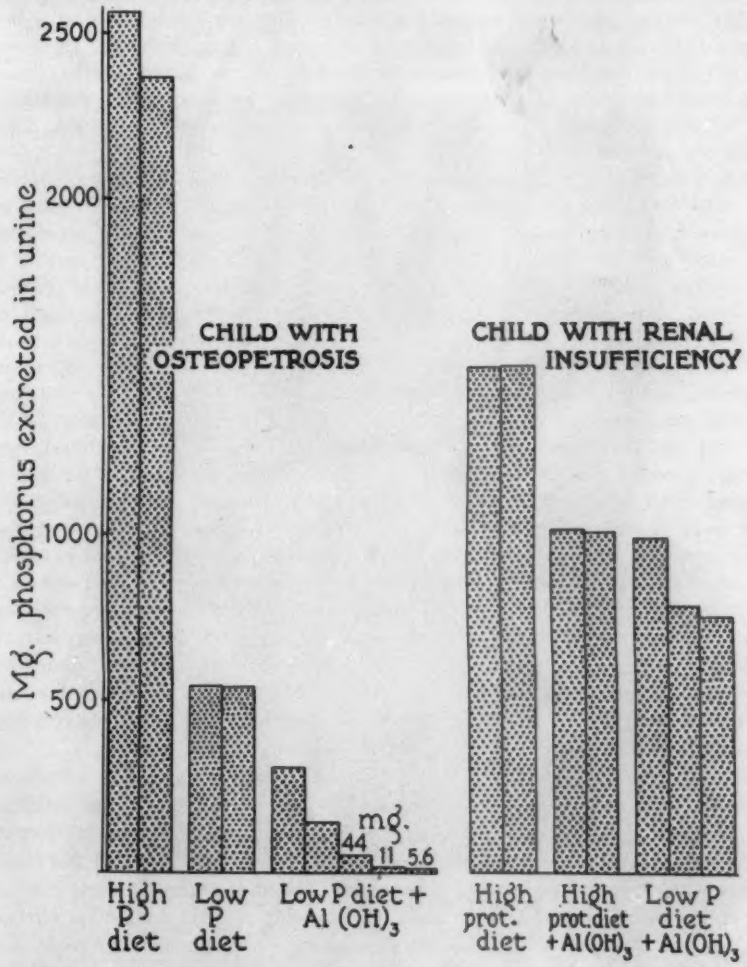


Fig. 2.—The effect of the phosphorus content of the diet and of aluminum hydroxide on the urinary excretion of inorganic phosphorus. Each column for the child with osteopetrosis, who had normal kidneys, indicates the amount of phosphorus excreted in one five day period, and each column for the child with renal insufficiency (case 1) indicates the excretion during a three day period.

10.9 and 7.6 mg., respectively. She was given a regular hospital diet, which contained 100 Gm. of protein, 80 Gm. of fat and 240 Gm. of carbohydrates and included 1 quart (946 cc.) of milk daily. No appreciable change in the calcium and inorganic

phosphorus content of the serum occurred with this regimen. The addition of 4 fluidounces (120 cc.) of 5 per cent solution of aluminum hydroxide daily to the diet caused a decrease in the inorganic phosphorus content of the serum from 7.6 to 6.3 mg. per hundred cubic centimeters. A comparable value for the serum inorganic phosphorus (6.5 mg.) was obtained by the use of a diet low in phosphorus. The low phosphorus diet provided 30 Gm. of protein, 50 Gm. of fat and 180 Gm. of carbohydrate. The inorganic phosphorus content of the serum was further lowered (while the patient was fed this diet) by the addition of 4 fluidounces (120 cc.) of 5 per cent solution of aluminum hydroxide daily. In figure 1 the effect on the inorganic phosphorus content of the serum of the reduced absorption and intake of phosphorus is illustrated. In figure 2 the reduction in the urinary excretion of inorganic phosphorus which accompanied the dietary alterations is shown.

The patient was free from symptoms and returned home. The low phosphorus diet with the addition of aluminum hydroxide was adhered to indifferently well for three months and was finally discontinued. After consuming for approximately one month a liberal family diet which included a quart of milk daily, pains in her extremities, somnolence, vertigo and bouts of headaches, nausea and vomiting developed. As her illness progressed, she began to have spontaneous nosebleed, bleeding from the gums, bloody vomitus and tarry stools. Her blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic, and the urine still showed albumin. At this time the value for the nonprotein nitrogen of the blood was 200 mg. per hundred cubic centimeters, that for the serum calcium was 7.4 mg. and that for the serum inorganic phosphorus 11.9 mg. Repeated blood transfusions failed to stop the bleeding. The serum calcium decreased to 6.2 mg. per hundred cubic centimeters. The ascorbic acid index and prothrombin clotting time were always within normal limits. Vitamin K was administered, without effect on the bleeding. Again a low phosphorus diet was employed, and in addition 20 Gm. of calcium lactate in fruit juice was administered daily. Iron and ammonium citrates and the liver extract low in phosphorus were further supplements of the diet. No additional transfusions were given. In two days the bleeding decreased noticeably and in four days had stopped completely, the lassitude disappeared and the child was ambulatory in two weeks. In figure 1 the broken line indicates the reduction in the inorganic phosphorus content of the serum which resulted from the use of the low phosphorus diet and calcium lactate.

During the eight months which have elapsed since her last acute episode this child has been maintained on a relatively low phosphorus diet (one essentially free of dairy products), without aluminum hydroxide, and has been in relatively good health, as evidenced by her regular attendance at school and her ability to play with other children and to roller skate. The most recent chemical examination on her blood (Oct. 10, 1940) gave the following results; nonprotein nitrogen, 133 mg. per hundred cubic centimeters; calcium, 8.85 mg., and inorganic phosphorus, 6.5 mg.

CASE 2.—D. A., a 6 year old white boy, was admitted to the hospital Nov. 24, 1939. He had had coryza, cough, fever and earache for five days. Two days before admission he had a generalized convulsion, which was followed by delirium, deep breathing and vomiting.

Past History.—The birth and feeding histories were normal. He had had 1 teaspoon of cod liver oil daily during the first year of life and 1 tablespoon daily since. Since the age of 4 months the boy had been subject to occasional generalized convulsions. These convulsions were not necessarily associated with fever or with other evidence of infection. Phenobarbital had been given for the

past nine months, and during this time he had had only one convulsion. One month prior to hospitalization he began to complain of pains in his ankles when he stood or walked.

Examination.—The child was comatose and appeared small for his age. He could be aroused with difficulty. The throat was acutely inflamed, and both tympanic membranes were red and bulging. His temperature was 102 F. He had slight secondary anemia and albuminuria.

Course.—The acidosis was treated for several days with fluids, including milk, without evidence of improvement. Chemical examination of the blood at this

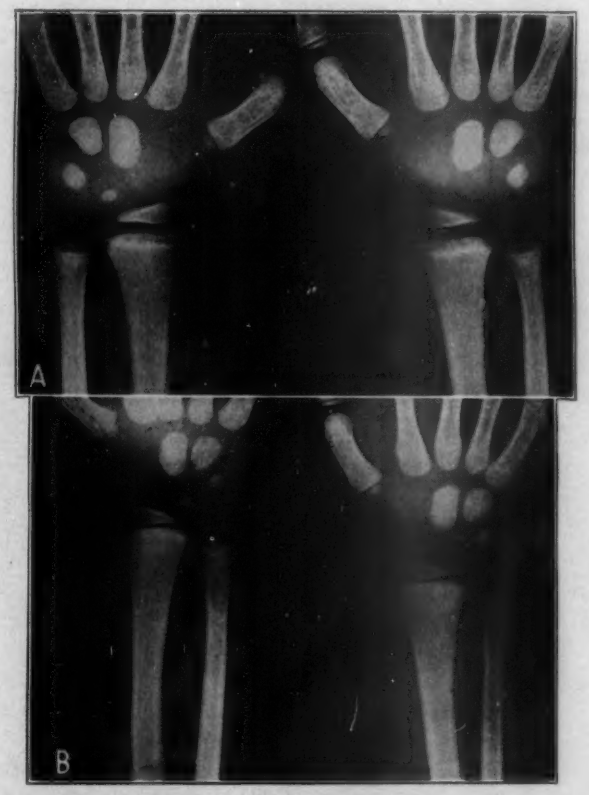


Fig. 3 (case 2).—*A*, changes in the distal ends of the radiuses and ulnas, and *B*, appearance of same bones three months later, when the lesions had healed.

time showed the nonprotein nitrogen content to be 200 mg. per hundred cubic centimeters, the serum calcium 5.1 mg., the serum inorganic phosphorus 13.4 mg. and the carbon dioxide-combining power 18.2 volumes per cent. The albuminuria persisted. Renal function was poor, and during the long period of coma distention of the bladder, with the overflow of incontinence, developed. Because of the pains in the joints, the high concentration of inorganic phosphorus and the low concentration of calcium in the serum and the impaired renal function, renal rickets was suspected. Roentgenograms of the long bones revealed irregular metaphysial calcification, which indicated impaired calcification or resorption of bone in this area (fig. 3 *A*).

A diet relatively low in phosphorus was constructed by omitting all dairy products. Three grams of calcium gluconate daily was added to the diet. Sodium bicarbonate was given orally for five days. Two fluidrachms (7.39 cc.) of cod liver oil was also included in the diet. Within a week the acidosis disappeared, the nonprotein nitrogen of the blood was lowered to 74 mg. per hundred cubic centimeters, the serum calcium was increased to 7.6 mg. and the serum inorganic phosphorus was decreased to 4.2 mg. At this time there was no distention of the bladder; an intravenous pyelogram failed to visualize the kidneys or the ureters, and there was little dye in the bladder one hour after its injection. A

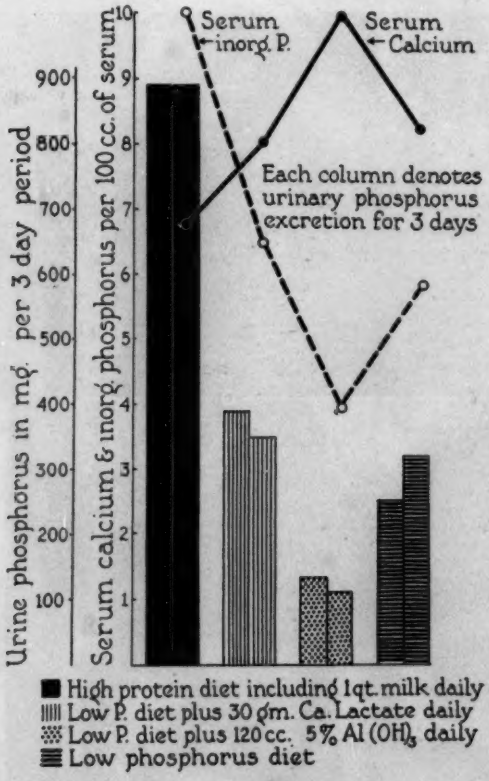

Urine phosphorus in mg. per 3 day period
Serum calcium & inorg. phosphorus per 100 cc. of serum
Serum inorg. P.
Serum Calcium
Each column denotes urinary phosphorus excretion for 3 days
High protein diet including 1qt. milk daily
Low P. diet plus 30 gm. Ca. Lactate daily
Low P. diet plus 120 cc. 5% Al (OH)3 daily
Low phosphorus diet

Fig. 4 (case 2).—The relative effect of diet alone and of diet plus the ingestion of calcium lactate or aluminum hydroxide on the excretion of inorganic phosphorus in the urine and on the concentration of inorganic phosphorus and calcium in the serum, determined during each regimen.

diagnosis of renal infantilism with renal rickets was made. The reduction of the serum inorganic phosphorus which resulted from the low phosphorus diet is indicated by the solid line in figure 1, which also shows the effect on the serum inorganic phosphorus of restoring milk to the diet.

The child continued to improve on the low phosphorus diet and was allowed to go home. Three months after this regimen was begun, roentgenograms of the wrists showed healing of the lesions in the bones (fig. 3 *B*).

Soon afterward the mother grew lax about restricting the diet and added milk, cheese and ice cream to it. At this time the serum calcium was 8.9 mg. and the inorganic phosphorus had risen to 10.4 mg. per hundred cubic centimeters. The patient was readmitted to the hospital so that it might be determined whether the concentration of phosphorus in the serum could be materially altered. The results of this study are given in figure 4. The values for the concentrations of calcium and inorganic phosphorus in the serum demonstrate an inverse relation between these two constituents. The values for the excretion of phosphorus in the urine show that a diet low in phosphorus with the addition of aluminum hydroxide is more effective in reducing the urinary phosphorus than either a low phosphorus diet alone or such a diet given in combination with relatively large amounts (30 Gm.) of calcium lactate daily.

Nine months have elapsed since the low phosphorus diet was instituted. The child has continued to have albuminuria but has felt relatively well, has attended

Fig. 5 (case 3).—Areas of irregular calcification visible at the distal metaphyses of the tibias and fibulas.

school regularly and has had no recurrence of the bone lesions. The most recent examination of the blood (Oct. 16, 1940) gave these values: nonprotein nitrogen 100 mg., serum calcium 8.7 mg. and serum inorganic phosphorus 5.7 mg. per hundred cubic centimeters.

CASE 3.—D. H., a white boy 8 years of age, was admitted to the hospital on Oct. 25, 1939 because of weakness, pallor and albuminuria. When he was 3 years old he had scarlet fever, and four months later, when he underwent tonsillectomy, he had albuminuria. Repeated examinations during the succeeding five years showed persistence of the albuminuria and occasionally granular casts and blood in the urine. During the past year his appetite had been poor and there had been some edema of the eyelids. Three months prior to admission he complained of headache and pain in the ankles. He was retarded in growth (height, 43 inches [46 cm.] and weight, 41 pounds [18.6 Kg.]), pale and listless. The ankles were tender and the feet pronated. There was a 30 per cent enlargement of the heart to the left, according to the roentgenogram, and a loud, harsh apical systolic murmur, trans-

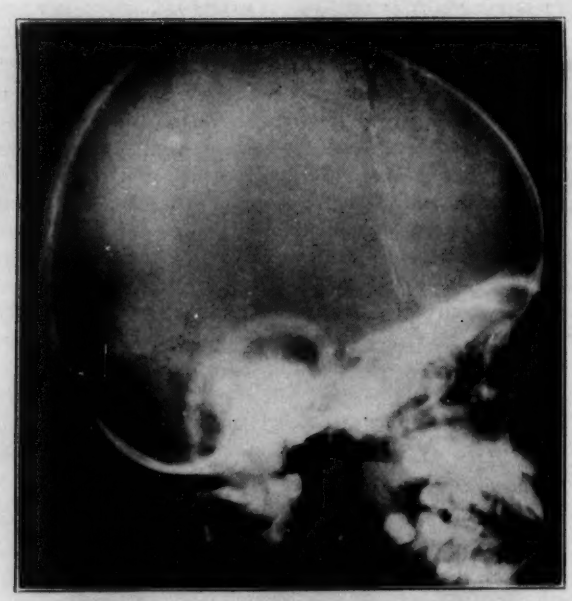


Fig. 6 (case 3).—Illustration of the hazy appearance which the calvarium may have when irregular calcification and decalcification are occurring.

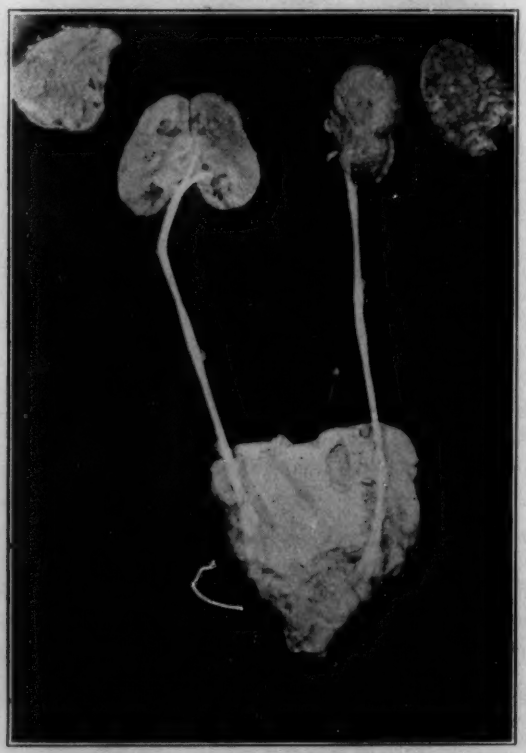


Fig. 7 (case 3).—The kidneys, bladder and adrenals, showing that the kidneys were of about the same size as the normal-sized adrenals.

mitted to the left, was present. His blood pressure was 120 mm. of mercury systolic and 78 mm. diastolic. The blood count showed a hemoglobin content of 54 per cent (Sahli), 2,300,000 red cells and 8,600 white cells, with a normal differential count. Examination of the urine showed a specific gravity of 1.005, albumin (2 plus) and a few granular casts. The nonprotein nitrogen of the blood was 135 mg. and the cholesterol 286 mg. per hundred cubic centimeters. Intravenous and retrograde pyelograms failed to outline the ureters or the pelves or calices of the kidneys. Although in many respects the clinical picture was that of renal infantilism, the albuminuria which followed the attack of scarlet fever could not be ignored, and chronic nephritis seemed the most likely explanation of the renal insufficiency.

Treatment consisted in giving repeated blood transfusions, feeding a high protein diet and administering iron and ammonium citrates. After one month

TABLE 2.—*Effect of Diet and the Administration of Aluminum Hydroxide on the Inorganic Phosphorus Content of the Blood and the Urine* *

Period †	Diet	Medication	Blood, Mg. per 100 Cc.	Serum, Mg. per 100 Cc.		Urine, Gm. per 100 Cc.
			Nonprotein Nitrogen	Calcium	Inorganic Phosphorus	Inorganic Phosphorus
1	Regular, with no milk	.....	123	9.3	13.1	0.415
2	Regular, with no milk	.....	127	9.6	12.0	0.497
3	Regular, with milk	120 cc. of aluminum hydroxide daily	...	...	....	.....
4	Regular, with milk	120 cc. of aluminum hydroxide daily	104	9.5	8.2	0.242
5	Low phosphorus ‡	5 Gm. of calcium-lactate daily	...	...	....	0.336
6	Low phosphorus	5 Gm. of calcium lactate and 6 Gm. of sodium bicarbonate	100	8.46	9.42	0.342

* These data are for D. H. (case 3).
† Each observation period was three days long.
‡ The low protein diet contained 180 Gm. of carbohydrate, 60 Gm. of fat and 30 Gm. of protein.

in the hospital the patient was instructed to eat a diet high in protein (this included liberal amounts of dairy products) and was sent home. During the following six months there developed frequency of urination, more severe pains in the legs, twitching of the muscles of the legs and inability to relax. The mother of this child had conversed with the parents of the patients in cases 1 and 2 and requested similar treatment for her child.

He was again admitted to the hospital on July 9, 1940. A review of the history and the data from examinations of the blood and urine suggested that this child might have renal rickets. Roentgenograms and chemical examinations of the blood gave further evidence that this impression was probably correct. There was a slight patchy loss of density of the bones of the upper and lower extremities, with subepiphysial decalcification or acalcification of both tibias and fibulas at the ankle (fig. 5). Similar but less severe changes were present in the wrists and the phalanges of the feet. The tables of the calvarium were thick and had a ground glass appearance (fig. 6). The blood count showed marked

anemia—a hemoglobin content of 6.64 Gm. per hundred cubic centimeters (Newcomer) and 2,300,000 red cells. The nonprotein nitrogen content of the blood was 115 mg. per hundred cubic centimeters, the serum calcium was 9.6 mg. and the serum inorganic phosphorus was 8.8 mg. Three transfusions resulted in a temporary increase in the number of red cells and in the hemoglobin content of the blood. It was hoped that the mild uremia might be relieved and the renal rickets healed by the use of a low phosphorus diet in conjunction with aluminum hydroxide. Before the anorexia and dietary idiosyncrasies had been overcome

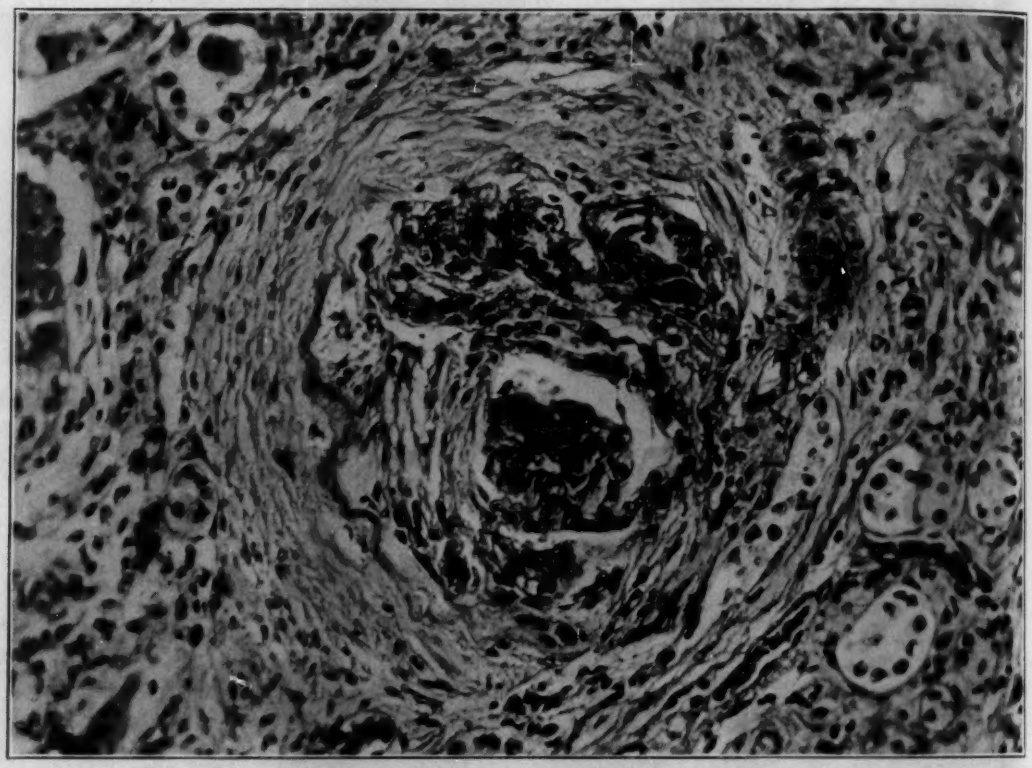


Fig. 8 (case 3).—Glomerulus of the kidney, showing the proliferation of the endothelial cells, the thickening of Bowman's capsule and the periglomerular fibrosis. High magnification.

the uremia became worse, the patient refused practically all food and he soon became first edematous, then comatose and died.

The results of the incomplete metabolic study on this child are given in table 2. The data show that there was a reduction in the inorganic phosphorus content of the serum and the urine when aluminum hydroxide was added to a diet containing moderate amounts of phosphorus. A greater decrease was obtained by using the moderate diet with the addition of aluminum hydroxide than by giving a diet low in phosphorus without the hydroxide.

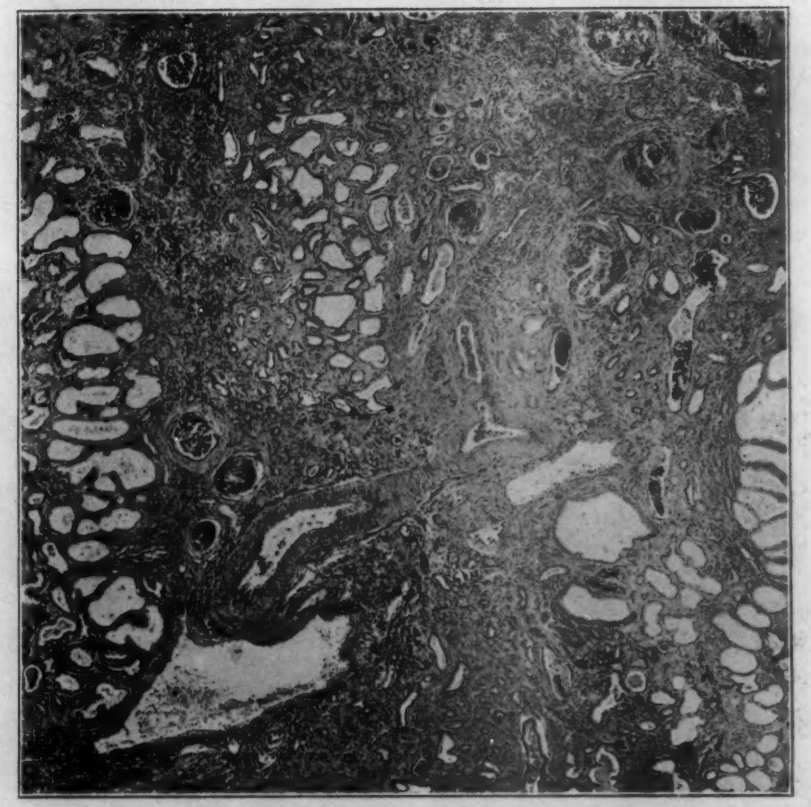


Fig. 9 (case 3).—Section of kidney, showing many dilated tubules and generalized replacement of parenchymatous tissue by fibrous tissue. Low magnification; hematoxylin-eosin stain.

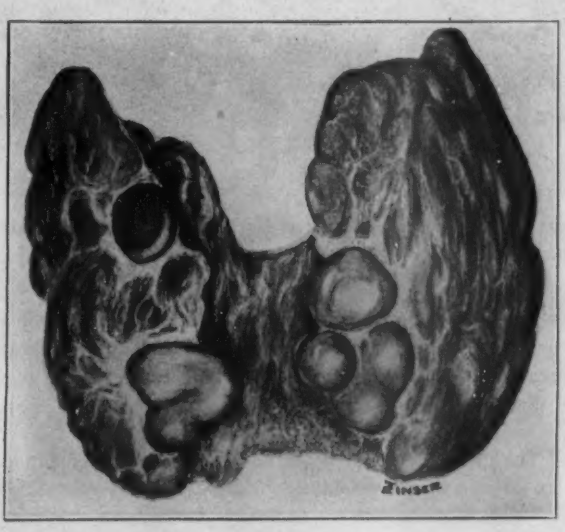


Fig. 10 (case 3).—Sketch showing the position and relative sizes of the enlarged parathyroid glands and the thyroid gland.

Autopsy.—The significant pathologic conditions disclosed were: bilateral chronic glomerulonephritis, renal rickets (renal osteitis fibrosa), generalized hyperplasia and hypertrophy of the parathyroid glands and cardiac hypertrophy and dilatation.

Kidneys: The kidneys were firm and of about one-fourth normal size (fig. 7), the right weighing 12 Gm. and the left 15 Gm. The capsule was adherent. On section the tissue was pale and dotted with small cysts, and the demarcation between the narrow cortex and the medulla was indistinct. The pelves of both kidneys were double, uniting outside the hilus to form one ureter. There was

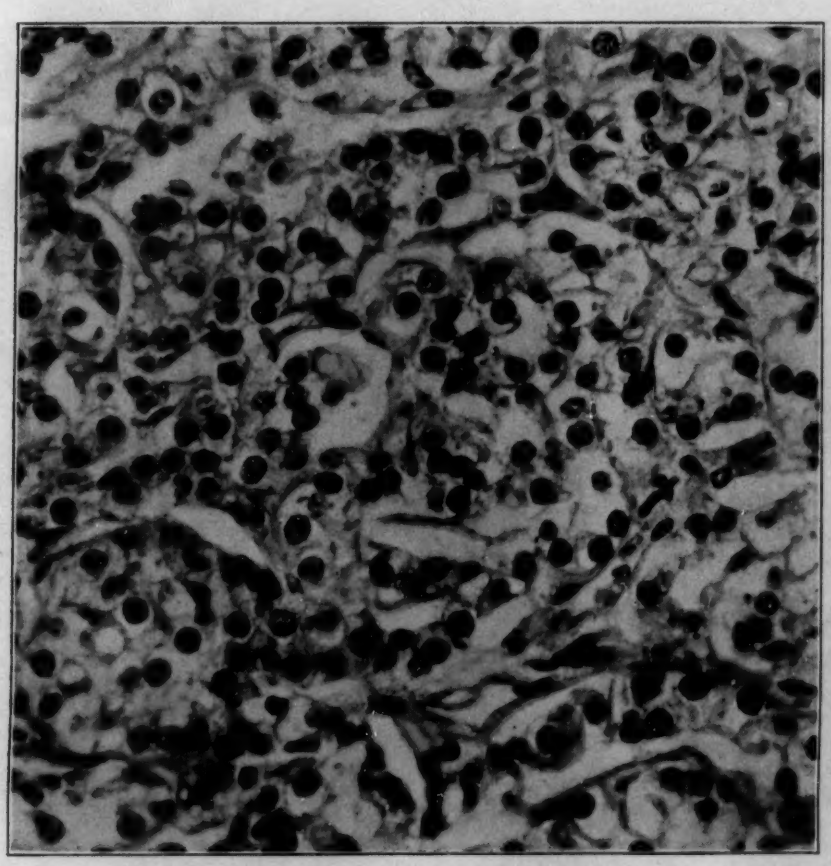


Fig. 11 (case 3).—Section of parathyroid tissue, showing cells with vacuolated or "water clear" cytoplasm.

no obstruction of the ureters or the urethra. Microscopic examination showed that the cortex was extremely thin. There were a few enlarged glomeruli which still appeared to be functioning, but even the best preserved of these showed thickening of the basement membrane, fusion of the tufts and marked sclerosis of Bowman's capsule (fig. 8). The remainder showed marked scarring or complete atrophy. The tubules were far apart, and most of those remaining were widely dilated (fig. 9). Some tubules contained hyaline or leukocytic plugs. The blood

vessels were close together, and there were much scarring and thickening of their walls; occasionally the intima was thickened and hyalinized.

Parathyroids: There were two parathyroid glands on the left and a group of four on the right, each measuring 3 by 6 mm. (fig. 10). They were formed of trabecular masses of cells separated by a rich network of capillaries. A few cell columns showed alveoli. The cells were of almost uniform size and were large and round to polyhedral, with round nuclei; in type they ranged from pale vesicular cells with a clear cytoplasm (fig. 11) to deeply staining cells with a pale

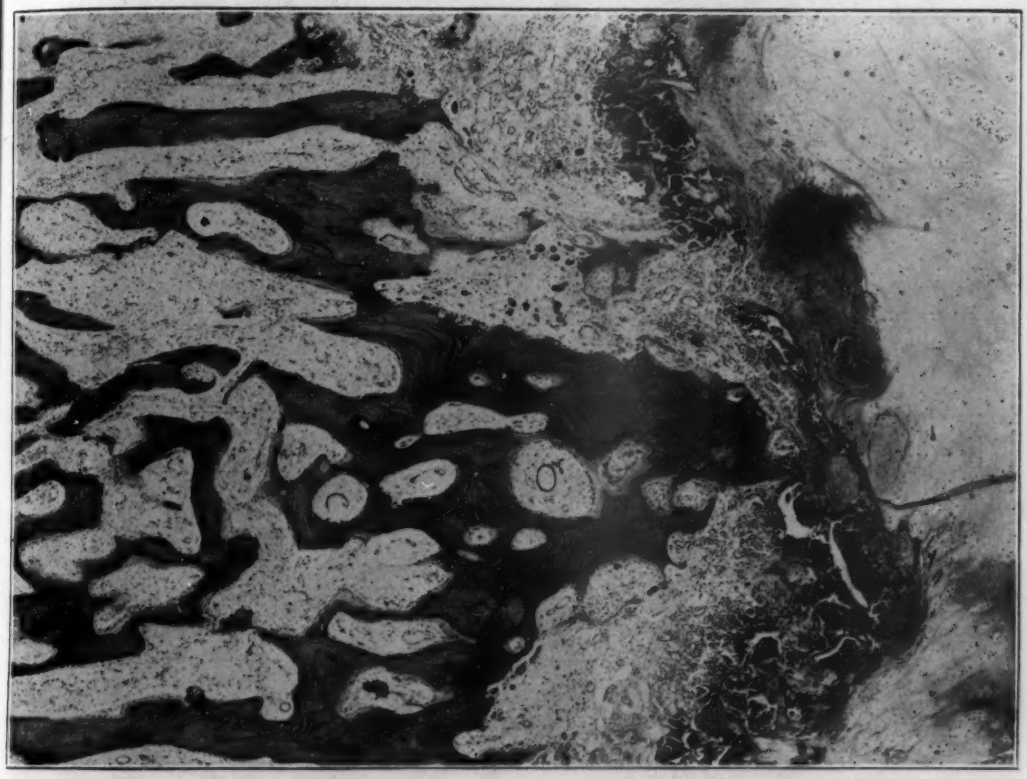


Fig. 12 (case 3).—Section of decalcified rib, showing the absence of regular columns of chondrocytes in the epiphysial cartilage, the generalized fibrosis of the marrow cavity, the bone resorption in the metaphysial zone and the numerous giant cells. Low magnification; hematoxylin and eosin stain.

eosinophilic cytoplasm and deeper eosinophilic granules. A few mitotic figures were noted.

Rib: The cartilage, as well as the bone, of the ribs showed changes (fig. 12). The regular, parallel rows of chondrocytes were absent; instead, there were small patches of proliferating cartilage cells in the area usually occupied by the calci-

fied cartilage, and these chondrocytes overlay, in an irregular line, a thick layer of proliferating vascular osteoid tissue, in which there was no evidence of organization except for the presence of irregular groups of osteoclasts. Many of these osteoclasts surrounded small spicules of bone which appeared to be undergoing resorption. There was a wide layer of osteoid tissue beneath the periosteum. Many of the spicules of cancellous bone ended in ragged edges of proliferating osteoblasts (fig. 13), leaving hazy outlines and giving the impression of active bone resorption, although not through osteoblastic activity. The marrow cavity was almost totally replaced by fibrous tissue which appeared osteoblastic in origin. Only a few scattered islands of hematopoietic cells were found.

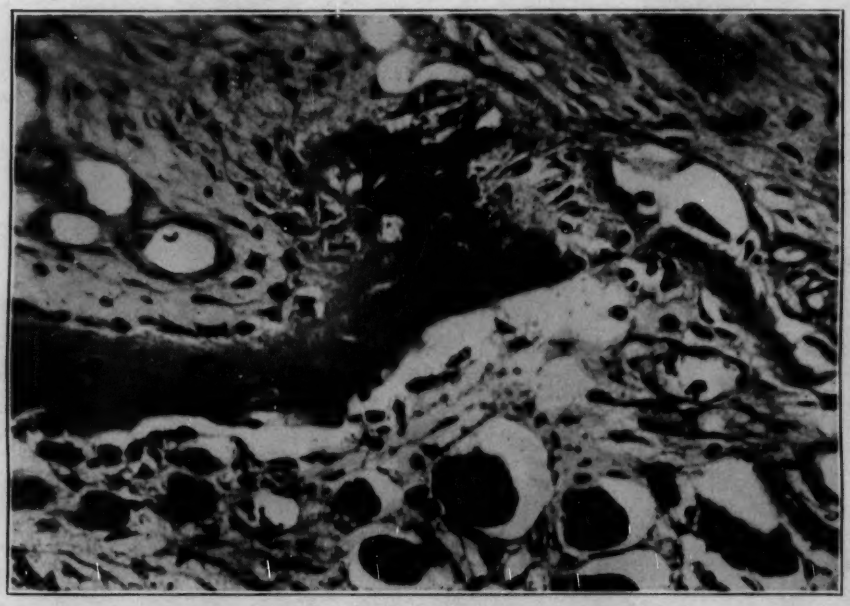


Fig. 13 (case 3).—Section of rib (higher magnification than in figure 12), showing fibrosis of the marrow space, osteoblastic proliferation, active resorption of a spicule of bone and numerous giant cells.

COMMENT

The diet prescribed for the treatment of patients with renal insufficiency due to nephritis has varied widely from one low [2a] to one high [11] in protein. No particular attention appears to have been directed to the importance of diet in cases of renal insufficiency due to causes other than nephritis, such as prolonged pyelonephritis or congenital anomalies. Park and Eliot [9] suggested the use of a diet high in calcium and low in phosphorus for patients with renal hyperparathyroidism, basing their

11. Aldrich, C. A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1938, vol. 3, chap. 28, p. 19.

suggestion on the experimental work of Shelling,[12] who demonstrated the importance of the phosphorus content of the diet in relation to the precipitation and the prevention of tetany in parathyroidectomized rats.

A diet low in phosphorus seems to be desirable for patients with renal insufficiency, irrespective of the cause of the impairment of renal function. The severity of the renal insufficiency should determine the amount of dietary restriction which is necessary. However, any restriction of diet may be made difficult by the fact that chronic renal insufficiency, especially when it is severe enough to produce an almost constant state of acidosis, is frequently accompanied by severe anorexia. Occasionally a child will refuse the foods allowed in a low phosphorus diet because of a strong desire for the prohibited dairy products. Starvation will increase the retention of phosphorus in the serum. Furthermore, some persons will not adhere to a strict diet. For these reasons the use of aluminum hydroxide or some other compound which interferes with the absorption of phosphorus and consequently permits the consumption of a more liberal diet appears desirable. The data presented here and elsewhere [4] provide ample evidence of the effectiveness of aluminum hydroxide in forming insoluble salts with phosphorus in the gastrointestinal tract. There are several variable factors which make it impossible to predict just how much phosphorus will be removed by the administration of a given amount of aluminum hydroxide. The formation of insoluble phosphates of this compound in the gastrointestinal tract appears to depend on a preliminary reaction of the hydroxide with the hydrochloric acid of the gastric juice so that a partial conversion to the chloride occurs. Thus gastric secretion, the buffering effect of the diet and probably the secretion of the pancreas all influence the extent to which insoluble aluminum phosphates will be formed in the intestine. Occasionally, a patient will vomit the aluminum hydroxide and will be nauseated by it whether it is taken during or after the meal. Gastric irritation probably is a factor in some cases, while in others there probably is a strong psychic element. Sometimes persuasion suffices to overcome these difficulties, and in other instances the low phosphorus diet alone must be depended on to reduce the retention of phosphorus. It may be possible to find a more reactive compound of aluminum which will not be correspondingly more irritating to the gastrointestinal tract. It would be desirable to have a compound of aluminum the presence of which in solution could be disguised completely and the ability of which to form insoluble phosphates in the intestine would be independent of gastric and pancreatic secretion. It has been our practice first to try to control the concentration of inorganic phosphorus and calcium in the serum by

12. Shelling, D. H.: J. Biol. Chem. **96**:195, 1932.

restricting the intake of phosphorus and by adding a moderate amount of calcium to the diet. The use of aluminum hydroxide has been restricted to the cases in which an adequate reduction in the inorganic phosphorus of the serum could not be obtained by dietary means and those in which the patient could not or would not conform to the restrictions necessary to make dietary control effective.

The use of a compound, such as aluminum hydroxide, as a means of reducing the retention of phosphorus should be applicable to any condition in which there is a pathologic elevation of the concentration of inorganic phosphorus in the serum or in which a reduction of urinary phosphates seems desirable. Hypoparathyroidism and renal insufficiency are two conditions which are frequently accompanied by an abnormal concentration of inorganic phosphorus in the blood. The beneficial effects of a low phosphorus diet in controlling the manifestations of hypoparathyroidism have been demonstrated experimentally for the rat by Shelling [12] and Jones [13] and clinically by Freyberg, Grant and Robb.[14]

In 1926 Briggs [15] demonstrated that there was a reduction in the phosphorus content of the urine of normal persons fed various calcium salts. Shohl [16] stated that the use of a diet high in calcium and low in phosphorus causes phosphorus to disappear almost completely from the urine. However, calcium as a means of reducing the retention of phosphorus has the disadvantage of being partially absorbed itself, and it is less effective than aluminum hydroxide. The difference in the effectiveness of the two compounds is demonstrated in figure 4. Helfet [17] has recently reported on the use of aluminum acetate in the treatment of a variety of diseases involving the bones. This author used small doses of aluminum acetate in conjunction with no less than 1 pint (473 cc.) of milk daily. The chemical data presented in his paper do not permit an evaluation of the extent to which the phosphorus metabolism was influenced in the patients studied, but the amount of aluminum administered does not appear adequate to alter the retention of phosphorus materially when taken with a diet which contained as much phosphorus as is provided by a pint of milk. Aluminum acetate is probably much more irritating to the gastrointestinal tract than is aluminum hydroxide.

The use of aluminum hydroxide in conjunction with a low phosphorus diet may effect such a low absorption of phosphorus that a

13. Jones, J. H.: J. Biol. Chem. **115**:371, 1936.

14. Freyberg, R. H.; Grant, R. L., and Robb, M. A.: Hypoparathyroidism: Treatment of Chronic Cases, J. A. M. A. **107**:1769 (Nov. 28) 1936.

15. Briggs, A. P.: Metabolic Aspects of Calcium Therapy, Arch. Int. Med. **37**:440 (March) 1926.

16. Shohl, A. T.: Mineral Metabolism, American Chemical Society, Monograph Series, New York, Reinhold Publishing Corporation, 1939, p. 340.

17. Helfet, A. J.: Brit. J. Surg. **27**:651, 1940.

negative phosphorus balance will result. This fact was clearly demonstrated in the case of a child with normal kidneys who was fed a diet low in phosphorus and given aluminum hydroxide. Values for the excretion of phosphorus in the urine of this child are shown in figure 2. It is apparent that phosphates practically disappear from the urine when there is sufficient diminution in the intake and absorption of phosphorus and when the renal function is normal. (A similar decrease in the amount of phosphorus excreted in the urine occurred when normal adult dogs were fed a low phosphorus diet.) However, this child's excretion of phosphorus in the feces increased as the output in the urine decreased, and by the end of the experiment there was a definitely negative phosphorus balance. This patient had osteopetrosis and had been studied in detail previously;[18] he had been shown to possess marked ability to retain calcium and, presumably, phosphorus, and attempts to produce a negative calcium balance by purely dietary means or by the use of parathyroid extract or ammonium chloride had failed without exception. Failure to reduce to a similar degree the excretion of phosphorus in the urine of the children with renal insufficiency may have been due to a difference in the extent of the reduction in the absorption of phosphorus, to a difference in the endogenous metabolism of phosphorus or to an inability of the kidney to control the excretion of phosphorus. According to Peters and Van Slyke,[19] "An increase in phosphate absorption or an increase in endogenous phosphate catabolism . . . will be evidenced chiefly by increased urinary phosphate output." Conversely, a decreased absorption of phosphate should be manifested by a decreased excretion of phosphate in the urine. An increase in the endogenous catabolism of phosphate might partially obscure the reduced excretion of phosphate secondary to decreased absorption.

The results shown in figures 1 and 4 indicate that exogenous phosphorus is of importance in influencing the level of inorganic phosphorus in the serum of patients with renal insufficiency. It is impossible to decide from the data obtained whether the reduction in serum inorganic phosphorus when aluminum hydroxide was added to the diet was entirely due to a reduced absorption of phosphorus or whether aluminum hydroxide also removed phosphorus from the tissues. In the majority of instances there was an increase in the serum calcium when the concentration of inorganic phosphorus in the serum was reduced if the

18. Clifton, W. M.; Frank, A. A., and Freeman, S.: Osteopetrosis (Marble Bones), Am. J. Dis. Child. **56**:1020 (Nov.) 1938.

19. Peters and Van Slyke,[7] 1931, vol. 1, p. 1108.

initial concentration of calcium was definitely lower than normal. In figure 1 it is shown that the normal concentration of inorganic phosphorus in the serum of a child with normal kidneys can likewise be reduced by a reduction in the absorption of phosphorus. Since this child does not have normal bones, he may not have normal ability to mobilize phosphorus. However, a similar diminution of the initially normal values for serum inorganic phosphorus of 2 normal adult dogs fed a low phosphorus diet for several months has been observed, and there was marked reduction of the concentration of inorganic phosphorus in the serum of puppies fed a diet low in phosphorus less than a month after the diet was instituted.

The deleterious effect of milk on the phosphorus content of the serum was demonstrated in cases 1 and 2, and the effects of removing it from and adding it to the diet in case 2 are illustrated in figure 1. At another time, the diet in case 2 was altered by the addition of 1 quart (946 cc.) of milk daily to a diet otherwise low in phosphorus. The concentration of inorganic phosphorus in the serum rose from 6.6 to 9.9 mg. per hundred cubic centimeters, and that of calcium dropped from 8.8 to 6.7 mg. Coincident with these changes in the blood headache and pains in the muscles of the thighs developed. At no time has it been possible to dissociate the alteration of the calcium-phosphorus ratio from manifestations of an altered neuromuscular irritability. The importance of the calcium content of the cerebrospinal fluid in uremia was indicated by the experimental results of Mason and his co-workers.[20]

The patient in case 2, who had renal rickets at 6 years of age, was cooperative in conforming to the dietary restrictions. With the use of a low phosphorus diet supplemented daily with 5 Gm. of calcium lactate, 800 international units of vitamin D (cod liver oil) and 0.75 mg. of thiamine hydrochloride, the bone lesions healed, the tenderness of the ankles and the cramping of the muscles disappeared and he was able to resume normal activities. It is well recognized that remissions and exacerbations of the symptoms of chronic renal insufficiency occur spontaneously, and for this reason it is difficult to decide whether a particular procedure has actually influenced the course of the disease. Bader [21] stated that the bone lesions of patients with renal rickets may heal spontaneously. However, the evidence of improvement in this child was symptomatic and chemical as well as roentgenologic.

---

20. Mason, M. F.; Resnik, H.; Minot, A. S.; Rainey, J.; Pilcher, C., and Harrison, T. A.: Mechanism of Experimental Uremia, Arch. Int. Med. **60**:312 (Aug.) 1937.

21. Bader, G. B.: J. Pediat. **4**:368, 1934.

In recent years it has been generally recognized that prolonged renal insufficiency is associated with enlargement of the parathyroid glands.[22] When bone changes are present the syndrome is called renal rickets or renal hyperparathyroidism. In 2 of the 3 cases (cases 2 and 3) of prolonged renal insufficiency presented in this paper, bone changes were apparent in the roentgenograms. In the last case necropsy showed enlargement of the parathyroids, small kidneys and osteitis fibrosa of the bones. Gross and microscopic examinations of the kidneys, coupled with the history and the clinical data, indicated that the renal insufficiency was due to chronic glomerulonephritis. Probably renal impairment which causes a long-standing and not too severe retention of phosphorus can produce renal rickets regardless of the cause of the renal incompetency.

With the progress of the osteoporosis and subepiphysial decalcification, deformities develop. The diagnosis is relatively simple in the late state of the disease. The importance of the early symptoms of skeletal involvement should be emphasized, for with dietary and other treatment these symptoms may be arrested and temporary healing effected. Recurrent muscle cramps associated with albuminuria should call attention to the possibility of disturbance of the calcium-phosphorus ratio which, if not corrected, will lead to more severe symptoms. Another relatively early complaint may be pain in the joints, particularly in the ankles, on standing or walking. Soon after the onset of pain, pronation of the feet and widening of the ankle joints develop. The pronation frequently brings such children to the orthopedic surgeon. A less frequent manifestation of renal rickets is thickening of the skull, also observed in case 3.

SUMMARY

The effect of a low intake or absorption of phosphorus on the concentration of inorganic phosphorus in the blood and urine of 3 children with chronic renal insufficiency and 1 child with normal kidneys has been described. A low intake or absorption of phosphorus resulted in a decrease in the concentration of inorganic phosphorus and an increase in the concentration of calcium in the serum of the children with renal insufficiency. Aluminum hydroxide has been shown to be effective in reducing the concentration of inorganic phosphorus in the serum and urine of the children with uremia as well as of the child with normal kidneys. There seemed to be a correlation between the concentrations of inorganic phosphorus and calcium in the serum and the clinical

22. Bergstrand, H.: Acta med. Scandinav. **54**:539, 1921. Pappenheimer, A. M., and Wilens, S. L.: Am. J. Path. **11**:73, 1935. Gilmour, J. B., and Martin, W. J.: J. Path. & Bact. **44**:431, 1937.

manifestations of the disease. The foregoing results present a rational basis for the use of a diet low in phosphorus in the treatment of children with phosphorus retention associated with renal insufficiency. Some of the difficulties and limitations involved in the use of a low phosphorus diet have been indicated. Pain in the muscles of the thighs and calves and in the joints has been pointed out as one of the relatively early manifestations of an elevation of the concentration of inorganic phosphorus in the serum associated with chronic renal insufficiency. Observations at autopsy in 1 of the cases of chronic renal insufficiency, in which there were bone changes, have been reported.

The staff of the Children's Memorial Hospital made the clinical material for this study accessible. Dr. Marian Barnes, resident pathologist of the hospital, performed the autopsy and provided comment in case 3. Mr. Charles Zinser, of the same institution, made the drawing of the thyroid-parathyroid apparatus in case 3. Mrs. Wally Coughlin took the photomicrographs.

Dr. David Klein, director of the Wilson Laboratories, provided the liver extract, and Merck & Co. supplied the thiamine hydrochloride and the Alba Pharmaceutical Co. the aluminum hydroxide used in this study.

CHARACTER OF CONGESTIVE FAILURE IN CHILDREN WITH ACTIVE RHEUMATIC FEVER

BERNARD J. WALSH, M.D.
WASHINGTON, D. C.
AND
HOWARD B. SPRAGUE, M.D.
BOSTON

That congestive failure in children with rheumatic heart disease is due to the presence of active rheumatic fever is now commonly recognized. Less well known, however, are the clinical features of heart failure in such patients. It is the purpose of this communication to describe these clinical features.

MATERIAL

More than 200 children and adults with congestive failure and rheumatic heart disease have been carefully observed and treated at the House of the Good Samaritan between 1920 and 1940. Of particular interest for this report are 44 members of the group who entered the hospital during the period from July 1, 1937 to April 1, 1940, who were subjects of special study. These 44 patients were between the ages of 3 and 15 years (average, 8.8 years). The length of the stay in the hospital varied from less than a month to four years (average, twelve months).

CLINICAL OBSERVATIONS

It has been our experience that the initial signs of cardiac failure in children suffering from rheumatic heart disease are enlargement of the liver and puffiness of the face and unexpected gain in weight (due to fluid retention). These signs appear as a rule in the order named.

Schwartz and Levy [1] reported that basal pulmonary rales were conspicuously absent in children with hepatic enlargement and edema due to cardiac failure. In our experience rales have not always been absent in such children. Their appearance in our cases, however, was limited to the terminal hours of a fatal rheumatic infection and to the infrequent patient in whom cardiac failure was sudden and marked by pulmonary edema, with rales and hemoptysis.

From the House of the Good Samaritan, Boston.

1. Schwartz, S. P., and Levy, J.: Digitalis Studies on Children with Heart Disease: Effects of Digitalis on Edema of Children with Rheumatic Fever and Chronic Valvular Heart Disease in Presence of Sinus Rhythm, Am. J. Dis. Child. **42**:1349 (Dec.) 1931.

In addition to these evidences of heart failure in children which have been described by other authors,[2] we have noted three of importance which have not heretofore been adequately emphasized: (1) the shift of the electrical axis to the right in the presence of prolonged heart failure, (2) the development of a diastolic gallop localized in the second and third interspaces at the left sternal border and (3) an early rise of venous pressure above normal.

Enlargement of the Liver.—From our review of the literature it appears that Schwartz and Levy [1] were the first to point out an increase in the size of the liver as an early sign of heart failure in children. In our experience it has been the initial clinical sign in each patient, appearing in many instances a week or more before other clinical evidences of heart failure. Similarly, when improvement has occurred the liver has remained palpable for some time after the peripheral edema has disappeared.

Postmortem examination of children who have died with active rheumatic fever and congestive failure has shown that the changes in the liver have followed a characteristic pattern (fig. 1). There has been a remarkable degree of chronic passive congestion with hemorrhagic central necrosis. In many instances the hemorrhage has been outstanding in degree and widespread in distribution. Some degree of fibrosis has occurred when the congestive failure has been present for several months.

Puffiness of the Face and Unexpected Gain in Weight (Fluid Retention).—Frequently the first apparent change marking the development of heart failure in children sick with rheumatic fever was swelling of the face. It occurred to some degree in all children with congestive failure, and in a few it was considerable, causing them to resemble patients with nephrosis (fig. 2). Bachmann [2a] in 1929 called attention to this manifestation of serious cardiac insufficiency in children. An unexpected gain in weight invariably was associated with the facial edema. A marked accumulation of fluid took place in some cases in a period of from twelve to twenty-four hours. Usually, however, it was a more gradual process, requiring one or more weeks before it became clinically evident. Pitting was not demonstrable until the retained fluid amounted to between 7 and 10 per cent of the body weight.

Bachmann [2a] differentiated children with heart failure into two groups, one marked by a "nephritic" appearance, associated with gen-

2. (*a*) Bachmann, H. A.: Clinical Types of Edema in the Heart Failure of Children, Arch. Int. Med. **43**:795 (June) 1929. (*b*) Levy, J.: Modes of Cardiac Insufficiency in Children with Heart Disease, Am. J. Dis. Child. **44**:1259 (Dec.) 1932. (*c*) Schwartz and Levy.[1]

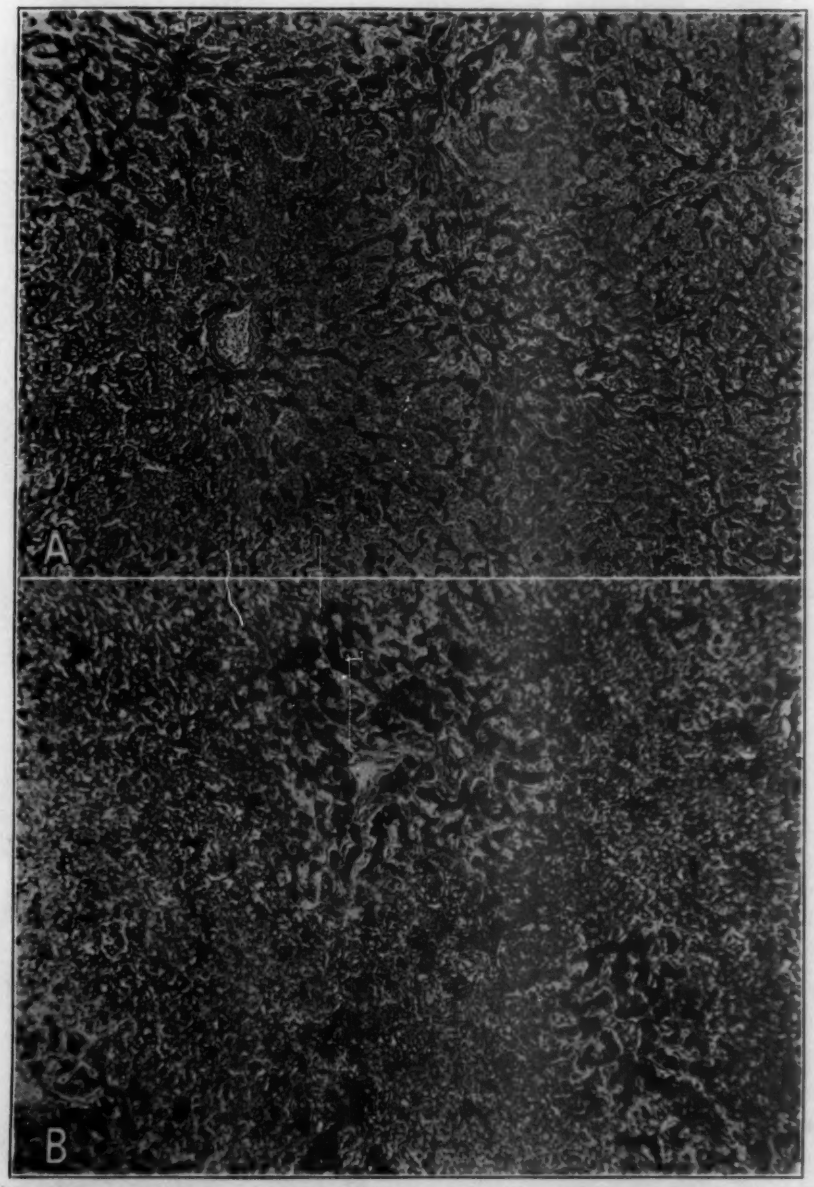


Fig. 1.—*A*, section of liver, illustrating a marked degree of passive congestion. The sinusoids of the liver lobules are markedly distended with blood, and the intervening liver cell columns are compressed. *B*, section of liver, illustrating extensive hemorrhagic central necrosis. Only small islands of visible liver tissue remain in the vicinity of the portal areas.

eralized edema (which this author considered to be "toxic" in origin), and the other by what he chose to call "the commonly recognized dependent type [of edema] involving the dependent portions of the body exclusively." He pointed out that those who had the greatest amount of edema, particularly about the face, appeared much less sick than those who had only a slight degree of facial edema. We, in agreement with Bachmann, have noted that the children with a large amount of edema of the face and extremities appear less ill than those with but slight edema of the face and that these children are comfortable in the flat, recumbent position. The probable explanation of this facial edema is that the children who are less severely ill and without orthopnea lie flat in bed without discomfort. This permits the gravitational equalifying of venous pressure over the entire body. As the head is then a relatively

Fig. 2.—Photographs of a 3 year old child, showing (*A*) facial swelling due to heart failure .twenty-four hours before the intravenous injection of 0.5 cc. of mercupurin, and (*B*) the appearance forty-eight hours after marked diuresis with loss of 4½ pounds (2,041 Gm.), initiated by the injection of mercupurin.

dependent portion of the body, edema fluid can accumulate there as readily as in the legs.[3]

Shift of the Electrical Axis to the Right.—There was a tendency to right axis deviation of the electrocardiogram in the presence of continuing heart failure even in patients with established aortic regurgitation. In an occasional electrocardiogram the degree of right axis deviation was marked, usually maximal during the time of greatest cardiac insufficiency. If recovery occurred, the electrical axis gradually returned to normal with the improvement and recovery of the patient

3. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1939.

(fig. 3). Figure 4 shows marked right axis deviation accompanying advanced congestive failure, a reversion to normal of the electrical axis when the heart failure disappeared and, finally, a return to moderate right axis deviation when heart failure reappeared. While there is no exact experimentally produced counterpart of these changes in electrical axis associated with heart failure in children, they are so much in keeping

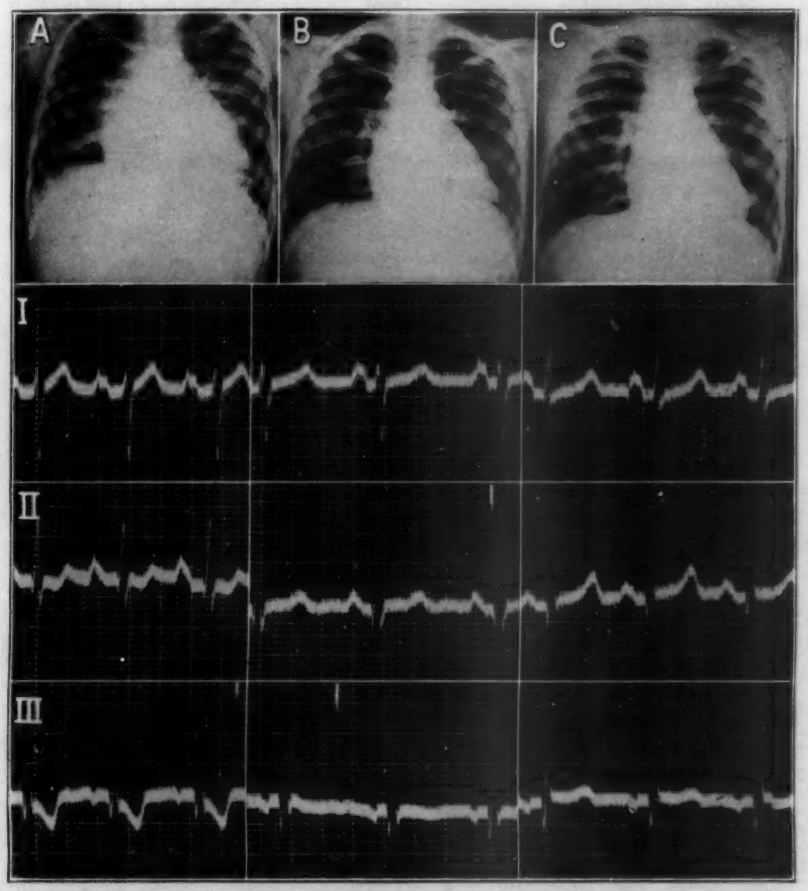


Fig. 3.—Roentgenograms and electrocardiograms of a 10 year old girl with rheumatic fever, rheumatic heart disease, mitral regurgitation and stenosis, aortic regurgitation and congestive failure. *A* shows the moderate enlargement of the heart and the marked right axis deviation during severe congestive failure evidenced by marked anasarca, enlargement of the liver and high venous pressure (225 mm. of physiologic solution of sodium chloride). *B* shows the decrease in the size of the heart and the lesser degree of right axis deviation two months later. The venous pressure was normal at this time, and there was no clinical evidence of congestive failure. *C* shows the normal-sized heart and normal electrical axis three and a half months later, shortly before the patient's discharge from the hospital in excellent condition and free of all evidence of rheumatic fever.

with the clinical picture of predominant failure of the right side of the heart that it seems to us correct to assume that they are good evidence of cardiac strain of the right-sided type.

Diastolic Gallop.—A few children with heart failure, probably not more than 1 in 5, have shown a well marked diastolic gallop, best heard in the second and third interspaces at the left sternal border. This is an additional important point of evidence in support of our belief that insufficiency of the right ventricle is the underlying physiologic cause of the early rise in venous pressure, enlargement of the liver, peripheral edema, freedom from rales and absence of orthopnea in some patients.

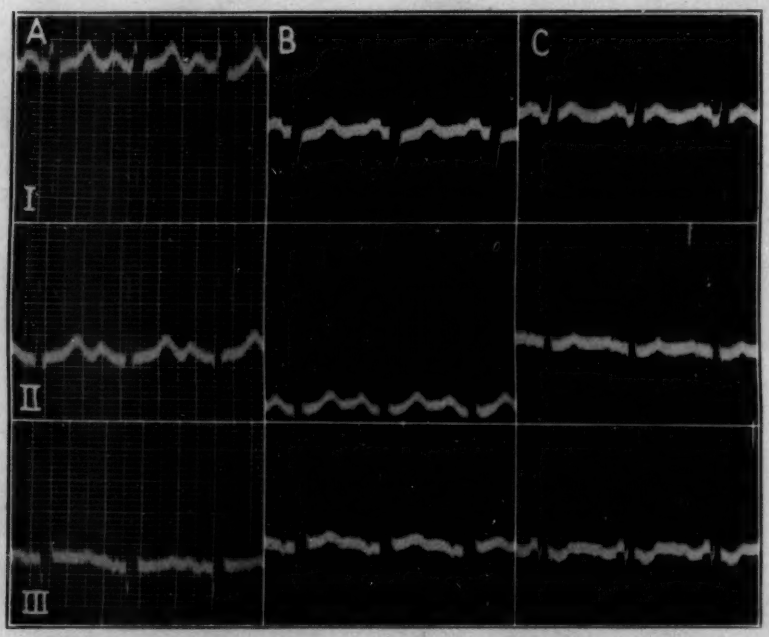


Fig. 4.—Electrocardiograms of a 13 year old girl with rheumatic fever, rheumatic heart disease with mitral regurgitation and stenosis and congestive failure. *A*, marked right axis deviation six weeks after the appearance of advanced congestive failure. *B*, normal electrical axis seven and a half months after the disappearance of congestive failure, although rheumatic fever continued to be active during this time. *C*, moderate right axis deviation five days before death. Congestive failure had again become apparent a month before.

Elevation of the Venous Pressure.—In our study of the dynamics of the circulation in these young patients with heart failure and rheumatic fever we have found that the invariable accompaniment of the previously mentioned signs was an elevated venous pressure. Repeated determinations of the venous pressure at various times for many patients revealed that it rose above normal concomitantly with enlargement of

the liver when heart failure developed in a child with rheumatic fever. In no instance did we detect enlargement of the liver in a young patient suspected of myocardial insufficiency in whom the venous pressure as measured in the antecubital vein was normal or below (normal is 50 to 150 mm. of physiologic solution of sodium chloride). In the presence of even slight enlargement of the liver the venous pressure was 180 mm. or above and was commonly found to be 225 to 300 mm. Obvious engorgement of the veins of the neck, however, was strikingly absent in spite of abnormally high venous pressure. After diuresis and subsidence of edema subsequent to the use of a diuretic or digitalis, the venous pressure promptly decreased, and in those cases in which all evidences of congestive failure disappeared it returned to within normal limits. In the absence of local venous occlusion, cardiac compression and tricuspid stenosis or regurgitation, an abnormally high venous pressure can be related only to right ventricular failure. While observers have probably assumed that the venous pressure was above normal in children with heart failure, this sign has not been accorded its proper place among the physiologic characteristics of heart failure in children. The fact that we have found a significant rise in venous pressure just as soon as heart failure was suspected and that it occurred in the absence of pulmonary rales and orthopnea is reliable evidence that heart failure in children is chiefly of the right ventricular type. That pulmonary rales are absent in children though all other evidences of an advanced degree of heart failure are present was first described as characteristic of congestive failure in children by Schwartz and Levy.[1] Our experience is in entire agreement, since we have but seldom heard rales in children with heart failure except in the few instances that we have mentioned, when heart failure was of the left ventricular type, as evidenced by pulmonary edema with rales and hemoptysis. We believe the explanation for this lies in the fact that most of the passive congestion due to failure of the right ventricle occurs in the liver and in the peripheral circulation rather than in the lungs. Though there is undoubtedly left ventricular failure, as indicated by orthopnea, it is relatively much less in degree and effect than is the failure of the right ventricle. A few of our patients (10 per cent) had orthopnea as an early manifestation of congestive failure, but in the majority (70 per cent) it appeared days or weeks after the other signs and frequently forecast a fatal termination of the disease. In 20 per cent it did not occur at any time, even though enlargement of the liver, anasarca and ascites were present.

We believe that the mechanical effect of the marked enlargement of the heart may be partly responsible for the position assumed by the child in the terminal stages. Characteristically, the patient leans forward over the bed table.

Other Considerations.—The amount and distribution of edema in many children with rheumatic heart disease and congestive failure causes them to resemble patients suffering from (1) nephritis or nephrosis, (2) hypoproteinemia with anasarca or (3) beriberi. However, we have found no evidence to indicate renal disturbance of sufficient degree to account for this clinical picture. Repeated urinalysis failed to disclose anything more than a few red blood cells or a slight trace of albumin in an occasional specimen. The serum protein levels of 5 patients, all of whom had evident pitting edema, enlargement of the liver and swelling of the face, ranged from 6.5 to 7.5 mg. per hundred cubic centimeters of blood. No patient had any collateral evidence of vitamin B deficiency. Two patients with typical congestive failure, as here described, were given large doses of a vitamin B_1 preparation (betaxin),[4] without alteration of the clinical course.

COMMENT

It is well known that the whole heart is affected during active rheumatic fever. This effect varies in degree. All parts do not share equally in the burden. In cases of mild rheumatic fever there may be little evidence except in the endocardium (valves).[5] In the cases of severe rheumatic fever the pericardium and, in particular, the myocardium are damaged.

Necropsy has provided no definite evidence that the right ventricle is affected to any greater degree than the left. In fact, Sacks[6] and Gross and Ehrlich[7] have found that in cases in which the patient died of active rheumatic fever Aschoff bodies were more numerous in the left ventricle than in the right. However, the sequence of events characteristic of congestive failure in children suggests that the right ventricle fails to a greater degree than does the left. A possible explanation for these clinical features is that the myocardium is weakened by the rheumatic infection and the right side of the heart, being fundamentally less strong than the left, fails more readily and to a disproportionately greater degree. We are aware, however, that the right ventricle has much less work to do than the left and that this is a serious weakness in our explanation. Gouley[8] has recently suggested that certain changes in the

4. Made by Winthrop Chemical Co., Inc.

5. Walsh, B. J.; Bland, E. F., and Jones, T. D.: Pure Mitral Stenosis in Young Persons, Arch. Int. Med. **65**:321 (Feb.) 1940.

6. Sacks, B.: The Pathology of Rheumatic Fever: A Critical Review, Am. Heart J. **1**:750, 1926.

7. Gross, L., and Ehrlich, J. C.: Studies on the Myocardial Aschoff Body: II. Life Cycle, Sites of Predilection in Relation to Clinical Course of Rheumatic Fever, Am. J. Path. **10**:489, 1934.

8. Gouley, B. A.: Evolution of Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion, Am. J. M. Sc. **196**:1, 1938.

parenchyma of the lungs due to rheumatic fever could account for the strain on the right side of the heart in patients with rheumatic heart disease. While such changes as he describes were present to some degree in our patients, we doubt that they can account wholly for heart failure in patients with rheumatic heart disease, particularly in those whose heart disease is of but a few months' or a few years' duration and whose lungs are reasonably free of changes at death.

CONCLUSIONS

The clinical features of congestive failure in children with rheumatic heart disease are described, the observations being based on a study of 44 children between the ages of 3 and 15 years who were seen between July 1, 1937 and April 1, 1940 at the House of the Good Samaritan.

The initial signs of heart failure in these 44 children with rheumatic fever and congestive failure were enlargement of the liver and puffiness of the face accompanied by unexpected gain in weight. A few children with congestive failure and active rheumatic fever preferred to lie flat in bed. These children had marked puffiness of the face, which caused them to look as if they had primary renal disease.

Pulmonary rales were seldom heard in these children, their appearance being limited to the terminal stages of the illness.

Other important evidences of congestive failure in children with rheumatic fever and congestive failure were high venous pressure apparent at the onset of the failure, a shift of the electrical axis of the heart to the right, which increased with progression of the heart failure and decreased or disappeared with the patient's improvement or recovery, and a well marked diastolic gallop rhythm along the upper left sternal border.

Case Reports

LATE RICKETS RESEMBLING THE FANCONI SYNDROME

JULIAN D. BOYD, M.D.
AND
GENEVIEVE STEARNS, PH.D.
IOWA CITY

With the recognition that rickets-like lesions may be found in association with derangements of metabolic processes, various syndromes of late rickets have been delineated, and the mechanisms involved have been subjected to study. In the clinic of the Children's Hospital we have had the opportunity during the past fifteen years to observe a number of children with late rickets and have been struck with the diversity of clinical patterns they have presented. Whereas certain groupings can be made on the basis of the apparent cause of the disorder, each patient has merited individual study because of the manner in which he has reacted to his difficulty. In general, the active rickets has seemed to be less significant in the patient's ultimate welfare than the underlying disturbance in metabolism.

The cases of some of the patients studied in this connection have been reported, and those of some others have been cited in society proceedings. Most of the data regarding these patients, however, both individual children and as a group, remain unreported. In view of the cumulated knowledge now available, it is planned to review the records of all patients with metabolic derangements associated with bone lesions, so that the salient points may be made available to others and analysis of the findings in the group as a whole made possible. This report deals with the cases of 3 children whose clinical pictures resembled most closely Fanconi's syndrome [1] but who presented outstanding differences among themselves.[2]

REPORT OF CASES

CASE 1.—In February 1925 W. J., a 7 year old white girl of Polish parentage, was brought to the hospital because of bony deformities and failure to grow. The

From the Department of Pediatrics, State University of Iowa College of Medicine.

1. Fanconi, G.: Jahrb. f. Kinderh. **147**:299, 1936.

2. These children's records were presented briefly at a meeting of the Central States Pediatric Society in 1926 (Boyd, J. D.: An Unusual Syndrome Associated with Rickets, Am. J. Dis. Child. **33**:539 [March] 1927) but have not been published heretofore.

family history was irrelevant. The child had been breast fed until a year of age and had never received cod liver oil; however, it was stated that even as an infant she was in the sunlight for significant periods. She had not learned to walk until she was 4 years old. Soon thereafter she broke her leg, but healing was prompt and walking was resumed. Teething probably had proceeded normally, but many of the deciduous teeth had been lost prematurely, not because of decay but because of resorption of the alveolar supporting structures.

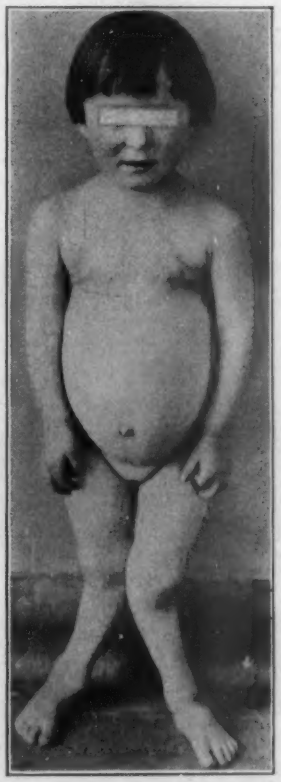


Fig. 1 (case 1).—W. J. at 7½ years of age. Her illness was diagnosed as active rickets, with dwarfism, glycosuria and chronic acidosis.

In addition to outstanding deformities residual to rickets, there was bulbous enlargement of the epiphysial zones of the wrists, the knees and the ankles (fig. 1). The child was decidedly small for her age; her height was 34½ inches (88 cm.) and her weight 30 pounds (13.6 Kg.). The cheeks were fiery red. Respirations were noisy, and there were evidences of chronic infection of the upper respiratory tract and of chronic bronchitis. The abdomen was prominent, evidently because of the generalized muscular weakness which was manifest.

The values for the calcium and the phosphorus of the serum were characteristic of active infantile rickets. Whereas the level of calcium was somewhat below

normal (9 mg. per hundred cubic centimeters), that of inorganic phosphorus was markedly lowered (1.75 mg.).

The child was placed on a regimen of vigorous antirachitic therapy, including administration of cod liver oil and ultraviolet radiation. Only after three

TABLE 1.—*Summary of Data for W. J.*

	Therapy			Data on the Blood							Recognized Urinary Abnormalities§	
Date, 1925	Ultraviolet Radiation*	Insulin †	Sodium Bicarbonate ‡	Calcium, Mg. per 100 Cc. of Serum	Inorganic Phosphorus, Mg. per 100 Cc. of Serum	Carbon Dioxide-Combining Power, Volumes per Cent	Sugar, Mg. per 100 Cc. Before Meal	Sugar, Mg. per 100 Cc. After Meal	Cholesterol, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Sugar, Gm. per 24 Hr.	Ketones ‖
2/27	..	..	..	9.0	1.8	....	...	...	...	....	?	?
3/ 2	+	..	..	9.0	1.5	....	...	...	...	....	?	?
3/10	+	..	..	8.6	2.8	....	...	...	...	....	?	?
3/22	+	..	..	10.0	2.9	....	...	...	...	....	?	?
4/ 5	—	..	..	12.0	3.5	....	...	...	...	....	?	?
4/29	—	..	..	8.2	4.5	....	...	...	...	....	?	?
5/ 7	+	..	..	8.9	3.0	....	...	...	...	....	?	?
5/18	+	..	..	10.2	3.1	....	...	...	...	....	?	?
6/ 4	+	..	..	9.7	5.1	....	...	...	207	....	?	?
6/18	+	..	..	12.4	5.9	....	...	...	207	....	?	?
6/23	+	..	..	....	...	....	...	173	...	....	+++	?
6/25	+	..	..	....	...	....	73	167	...	....	++	?
6/26	+	..	..	....	...	....	83	...	...	....	+++	?
7/13	+	..	..	....	...	....	103	...	...	....	44	++
7/15	+	..	..	....	...	....	...	250	...	....	24	+++
7/16	+	+	..	....	...	....	98	...	...	....	47	++
7/17	+	+	..	....	...	....	66	...	...	....	32	++
7/18	+	+	..	....	...	....	69	185	...	....	39	+
7/23	+	+	..	....	...	....	65	115	...	....	38	+
7/28	—	+	..	....	...	....	65	...	...	....	52	—
7/31	—	+	..	8.2	4.0	38.1	..	...	292	....	15	+
8/14	—	+	..	8.6	3.1	....	..	123	182	....	44	1.2
8/18	—	+	..	....	...	49.0	48	...	...	....	52	2.1
8/21	—	+	+	10.2	2.6	40.0	..	...	...	....	94	3.9
8/24	—	+	+	....	...	....	..	162	...	....	43	1.9
8/28	—	+	+	11.4	2.1	....	..	...	...	....	49	1.7
9/ 3	—	+	..	....	...	46.0	..	...	...	....	45	1.9
9/14	—	+	+	....	...	22.0	..	...	...	35.7	..	++

* Cod liver oil was given daily.
† The dose of insulin varied from 10 to 30 units daily.
‡ The dosage of sodium bicarbonate was 10 grains (0.65 Gm.) three times daily.
§ The average daily volume of urine during the six weeks prior to death was 1,380 cc.
‖ Ketones in the urine are expressed as grams of acetoacetic acid excreted in twenty-four hours.

months of that regimen, with ultraviolet therapy to the limits of cutaneous tolerance, did the serum phosphorus temporarily reach a level characteristic of healing rickets. Subsequently the level again fell, even with continued treatment.

Late in June, in the course of a clinical reevaluation of the patient's status, glycosuria was discovered. Subsequent analyses of the urine also were consistently positive for sugar, even though the levels of blood sugar throughout were

normal, low or, at the most, slightly elevated at the height of digestion. Whereas glycosuria had not been reported at her earliest examination, there is nothing to establish that this anomaly had developed while she was under observation. Subsequent to the discovery of glycosuria, the presence of marked ketonuria was established. This led to the discovery that the alkali reserve was chronically at an acidotic level. The ketosis and the acidosis were not affected significantly through the hypodermic use of insulin or through the administration of sodium bicarbonate by mouth.

Throughout her period of hospitalization the patient had frequent severe attacks of bronchitis, and this disease finally culminated in bronchopneumonia, with which she died in mid-September. No postmortem examination was permitted. At the time of death there still were clinical, chemical and roentgenographic evidences of active rickets.

In table 1 the biochemical data are listed. Figure 2 represents a roentgenogram of the wrist made after six weeks of antirachitic therapy.

Without more data it is impossible to appraise this child's condition accurately. However, from the evidence at hand, one can state that her illness

Fig. 2 (case 1).—Roentgenogram of the wrist of W. J. after two months of a regulated diet, administration of cod liver oil and ultraviolet irradiations.

was not an instance of rickets due to vitamin deficiency or to calcium starvation. There is no evidence that the child had renal insufficiency with resultant dwarfing and bone dystrophy. In many regards her case satisfies the criteria set up by Fanconi for the syndrome which bears his name. The chronic acidosis deserves comment, however. Fanconi stated that ketosis was not noteworthy in his subjects. In this case it was so striking that it produced or contributed to the existence of chronic acidosis. The role that such a state may play in aggravating bone dystrophy must be taken into consideration. Clinically, it seems unlikely, however, that ketosis or acidosis had been present for a prolonged period. Such a state probably would have been progressive and would have led to a fatal outcome. The degree to which it may have contributed to this patient's death cannot be appraised from the record. The child's small size and the medical history suggest that her difficulty had been present from infancy. With prolonged glycosuria, associated with difficulties in feeding or vomiting, the ultimate development of ketoacidosis in a patient with Fanconi's syndrome is not hard to visualize.

CASE 2.—R. W., a boy of 2½ years, was brought to the hospital because of inability to walk. His ankles and wrists had been markedly enlarged since early infancy, and deformities of the long bones and of the chest had developed at a correspondingly early period. His muscular performance had been poor at all times, and he never had attempted to walk. At the age of 9 months marked

Fig. 3 (case 2).—R. W. at 2½ years of age. His illness was diagnosed as active rickets, with dwarfism and glycosuria.

TABLE 2.—*Summary of Data on Blood of R. W.*

	Serum		Plasma Carbon Dioxide-Combining Power, Volumes per Cent	Whole Blood			
Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.		Sugar, Mg. per 100 Cc.	Sodium Chloride, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.
8/23	8.5	1.3	63	90	...	...	....
8/25	...	...	52	120	475	241	52.7
9/20	...	...	..	120	...	...	....
9/21	...	...	..	120	...	...	....
9/29	9.2	2.0	..	...	...	...	....

respiratory difficulty had developed, evidently caused in large part by the pliability of the thorax, and this had persisted ever since. His diet at all times had been markedly deficient; during the first year it was limited to feedings of sweetened condensed milk, and later he was given cow's milk in indeterminate amounts and, for six months prior to admission, food from the family table. Cod

liver oil had been prescribed recently, but it had been given only for the past four weeks, according to the father.

Possibly it is significant that the mother had been incapacitated for years by some form of rheumatism and that other members of the family also were afflicted. No details were obtainable from the record.

On admission to the hospital the patient weighed 15½ pounds (7 Kg.). The respirations were shallow, rapid and somewhat labored. Chronic bronchitis was clinically manifest. The distortion of the skeletal system was outstanding (fig. 3). The reactions to the Wassermann and the tuberculin test were negative. The level of calcium in the serum was below normal and that of inorganic phosphorus markedly lowered (8.5 and 1.3 mg. per hundred cubic centimeters, respectively). Roentgenograms of the bones showed marked osteoporosis, with multiple pathologic fractures and epiphysial signs of active rickets. The urine contained 2 per cent of dextrose.

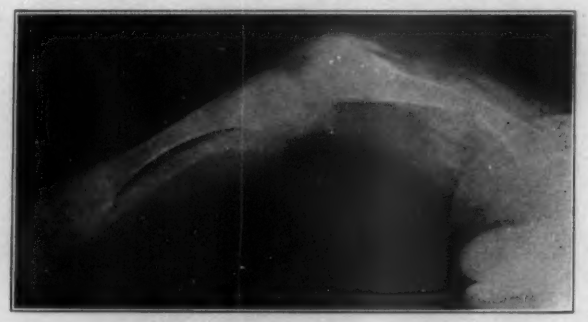


Fig. 4 (case 2).—Roentgenogram of the leg of R. W., taken at time of the first observation.

Under a therapeutic regimen, which included administration of cod liver oil and ultraviolet radiation daily, he showed no improvement. After a month, the level of calcium in the serum was 9.2 mg. per hundred cubic centimeters and that of phosphorus 2.0 mg., and glycosuria persisted. The patient had become progressively weaker and died about six weeks after entering the hospital. Postmortem examination was not permitted.

The laboratory data are summarized in table 2, and a roentgenogram of the leg is reproduced in figure 4.

CASE 3.—E. C., a boy of 8 years, came to the hospital because of difficulty in walking. He had been breast fed for the first fourteen months of life. At the time of weaning he began to walk, but it was noted that he was bow legged. A few weeks before admission to the hospital, weakness of the legs developed, and the genu valgum had become more pronounced. On several occasions he fell because of weakness and awkwardness in the use of his legs.

During childhood the boy's diet had not been obviously more defective than that of the average child. He had been accustomed to playing outdoors.

Fig. 5 (case 3).—E. C. at 8 years of age. His illness was diagnosed as active rickets, with polyuria, mild albuminuria and hypochloremia.

TABLE 3.—*Summary of Data for E. C.*

	Serum			Plasma		Whole Blood *					Urine			
Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Protein, Gm. per 100 Cc.	Carbon Dioxide-Combining Power, Volumes per Cent	p_H	Sodium Chloride, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Volume of Corpuscles	Albumin	Sugar	Volume (24 Hrs.), Cc.	Specific Gravity
4/28 9 a.m.	9.7	1.6	8.3	50	7.46	271	118	260	44.8	46%				
4/29.....	...	....	....	....	....	...	...	...	....	....	Trace	—	Day: 2,840 Night: 640	1.002-1.005
5/6 9:30 a.m.	9.5	3.4	8.7	63	7.48	288	...	210						

* Cytologic study gave normal results. Reaction to the tuberculin and the Wassermann test was negative.

There had been several isolated attacks of nausea and vomiting, associated with fever, jaundice and pale-colored stools. It is significant that for several years he had drunk large amounts of water and had voided proportionately.

Physical examination revealed a boy who was decidedly small for his age, measuring only 40 inches (102 cm.) in height. There were moderate rachitic deformities (fig. 5), and the epiphysial zones of the wrists, the knees and the ankles were enlarged. Otherwise the physical findings were not remarkable. Roentgenograms indicated active rickets of considerable intensity. The urine was

Figure 6

Figure 7

Fig. 6 (case 3).—Roentgenogram of the ankle of E. C., taken at time of the first observation.

Fig. 7 (case 3).—Roentgenogram of a section of the femur of E. C., made post mortem.

large in amount and of low specific gravity and showed a trace of albumin. Wassermann and tuberculin tests gave negative results. The amount of calcium in the blood was low normal, 9.7 mg. per hundred cubic centimeters of serum, and that of inorganic phosphorus was markedly reduced, 1.6 mg. After two weeks of vigorous antirachitic therapy, the values for calcium and phosphorus were 9.5 and 3.4 mg. per hundred cubic centimeters, respectively; roentgenograms

showed no signs of healing. Unfortunately, the patient contracted diphtheria while in the hospital, diphtheritic myocarditis developed and he died about a month after admission. At necropsy the kidneys and the other viscera showed only the changes one would expect to find associated with diphtheritic toxicosis. The bones showed interference with normal epiphysial mineralization.

Fig. 8 (case 3).—Photomicrograph of the osteochondral junction of the tibia of E. C.

The biochemical data for this patient are summarized in table 3, and the roentgenogram of the ankle obtained at the time of admission is reproduced in figure 6. Figures 7 and 8 show the appearance of sections of the femur and the tibia, respectively, prepared from specimens taken post mortem.

Attention is directed to the fact that the value for the serum calcium and the phosphorus of the serum parallel those for patients with infantile rickets, even though this boy's regimen and the other findings exclude the possibility of his

having active rickets caused by dietary deficiency. Also, the simulation of the findings characteristic of diabetes insipidus, with a reduced level of chloride in the serum, is significant.

COMMENT

These 3 cases of late rickets have certain factors in common. These include evidence of onset of the disease during infancy, retardation of growth of marked degree, hypophosphatemia which did not respond to the usual antirachitic measures, marked osteoporosis and rickets-like lesions in the epiphysial zones and undernutrition. From the metabolic standpoint the patients had rather dissimilar disturbances. R. W. (case 2) presented the most outstanding evidences of demineralization and was the youngest of the group. His associated metabolic dysfunction was characterized by glycosuria. Albuminuria and polyuria were not noted; the possibility that they were present and escaped detection cannot be established. He presented no ketosis, and his alkali reserve and blood sugar levels were normal. The other child who presented glycosuria, W. J. (case 1), did not have a larger urinary output than would be expected from the degree of glycosuria present. She had marked ketosis, which had led to acidotic levels of the blood constituents. There is nothing to suggest that the acidosis was dependent on renal dysfunction. There is no evidence to indicate that the glycosuria was due to diabetes mellitus; it was fairly constant in degree, did not fluctuate appreciably with the dietary intake or administration of insulin and was not associated with hyperglycemia.

The third patient, E. C. (case 3), was not glycosuric; his urine did contain moderate amounts of albumin. He had polyuria and polydipsia, with urine of low specific gravity. The other findings were not those associated with the usual form of renal dysfunction. There was no retention of nitrogenous metabolites. The kidneys at postmortem examination showed no histologic evidence of a chronic lesion, yet the possibility that minor chronic pathologic alterations were masked by the acute degenerative changes due to diphtheritic toxicosis must not be overlooked. The alkali reserve was normal. In view of the marked depression of the level of serum chloride, it is unfortunate that no data are available as to the complete electrolyte pattern of the serum or the urine.

Is it possible to consider the illnesses of these 3 children as examples of a common entity? To do so implies commonness of causation. Fanconi attributed the rachitic changes in his group of patients to renal dysfunction of a type different from that of patients with renal insufficiency, as exemplified by the renal dwarf. It is reasonable to suppose that disturbances of tubular function may give rise to alterations in renal elimination of such a nature that the mineral balance of the body is upset and demineralization arises. Albuminuria, renal glycosuria or polyuria could be accepted as evidence that tubular dysfunction was the basis of

the difficulty. Agencies remote from the kidney may cause similar derangements of metabolism, however. The nature of renal function may reflect the nature of the internal environment more than the status of the kidney as an excretory organ.

It seems probable that in certain instances late rickets is due to perversion of tubular renal function, just as in other instances it is associated with renal inadequacy of the usual type. However, it is equally apparent that extrarenal agencies which interfere with the normal metabolism of water or of electrolytes may cause demineralization of bone and interference with the normal formation of bone and may be associated with secondary evidences of renal dysfunction.

The etiologic classification of late rickets is not simple, nor can it be made on the basis of casual clinical or laboratory observations. Only through familiarity with the causative mechanism in each individual patient can therapeutic measures be directed into channels of maximum efficacy.

FETAL PERICARDITIS

SAMUEL T. KILLIAN, M.D.
CHICAGO

Pericarditis in the newborn is a distinct rarity, especially instances of the disease in which the pericardial cavity is completely obliterated. I have been able to find only 7 cases reported in the literature. Because of the rare occurrence of the condition it was thought of interest to report an additional case, in which a complete history of the mother and an opportunity to carry out a careful microscopic study of the infant's heart were presented.

Kelley,[1] in 1939, reported a case of fetal pericarditis occurring in a stillborn Negro girl, the product of twenty-two weeks' gestation. The visceral and the parietal pericardial surfaces were thickened and adherent, and when they were pulled apart there was disclosed between them a sticky, adhesive exudate. Microscopic examination showed that these surfaces were covered with a thick layer of granulation tissue, which was densely infiltrated with cells, mostly polymorphonuclear leukocytes. Between the visceral and the parietal pericardium was a thick exudate, formed of fibrin, many polymorphonuclear leukocytes, a few red blood corpuscles and lymphocytes. No bacteria were found, and microscopic study of the tissue failed to show any evidence of syphilis. In view of a history of gonorrhea in the mother and the father, it was suggested that the inflammation may have been of gonococcic origin. Kelley found 1 other instance of fetal pericarditis reported in the literature, that by Job, Lévy and Morlot [2] in 1927. Their patient was a full term infant who died four hours after birth. The pericardial sac contained 10 to 15 cc. of a serofibrinous exudate, and on the epicardial surface of the heart were small, opaque plaques. There was also acute verrucous endocarditis of the mitral and tricuspid valves. There was no report of a microscopic examination. Syphilis was suspected as the etiologic agent, since the infant had large areas of desquamation on the palms and soles. However, the Wassermann reaction of the mother's blood was negative.

This study was aided by a grant from the Otto Baer Fund.

From the Department of Pathology, Michael Reese Hospital.

1. Kelley, R. W.: Fetal Pericarditis, Arch. Path. **28**:248 (Aug.) 1939.

2. Job, Lévy and Morlot: Endo-péricardite du nouveau-né, Bull. Soc. d'obst. et de gynéc. **16**:171 (Feb.) 1927.

Five other cases of fetal pericarditis have been reported. Unfortunately, most of these reports were brief and contained no data from microscopic examinations. In 1829 Billard [3] observed the heart of a 2 day old child in which there were firm adhesions between the pericardial surfaces. He expressed the belief that the pericarditis was the result of an intrauterine inflammation. Hüter,[4] in 1857, reported the case of a premature infant who died twenty minutes after birth and in whom necropsy revealed adhesions between the epicardium and the pericardium, some of which could be pulled apart easily. Homolle,[5] in 1874, described a newborn child who had seropurulent pericarditis. The mother later died of a purulent infection. In 1925 Rascol and Thomas [6] reported a case of pericarditis in a boy who died suddenly eight hours after delivery. Postmortem examination revealed serofibrinous pericarditis. No other lesions were found. There were no signs of syphilis in the mother. They reported the case because they were unable to explain the pathogenesis of the pericarditis, but they suspected that syphilis was responsible. Reuss,[7] in 1927, mentioned an instance of fetal pericarditis in a premature stillborn child, the product of six months' gestation, who had been observed by Feller. The mother had influenza twice during the pregnancy. Necropsy showed severe adhesions between the two leaves of the pericardium. In addition, syphilitic osteochondritis and splenomegaly were observed.

REPORT OF A CASE

Maternal History.—A 20 year old, unmarried Negress presented herself at a maternity clinic and stated that she was about six months pregnant. Her health had been good prior to and during the pregnancy. There had been no previous pregnancies or miscarriages. The Kahn and Wassermann reactions of the blood at this time were positive. There were no physical signs pointing to syphilis, and the diagnosis made was "asymptomatic syphilis." Antisyphilitic treatment was started immediately, and she received a total of eleven injections of bismuth and nine of neoarsphenamine. The last two treatments were given about six weeks before delivery. She had no ill effects from the therapy. Labor began prematurely and she was delivered at home. Labor lasted less than twenty-four hours, and the delivery was uneventful. The placenta showed no gross changes. No Wassermann test was performed on the blood of the cord. The postpartum course was uneventful.

---

3. Billard, C.: Krankheiten der Neugeborenen und Säuglinge, Weimar, Landes-Industrie-Comptoir, 1829, p. 502.

4. Hüter, C. C.: Ueber die Verwachsung des Herzbeutels mit dem Herzen während des Uterinlebens, Deutsche Klin. **9**:63, 1857.

5. Homolle, M.: Péricardite purulente chez un nouveau-né, Bull. Soc. anat. de Paris **49**:745, 1874.

6. Rascol and Thomas: Péricardite chez un nouveau-né, Bull. Soc. d'obst. et de gynéc. **14**:504, 1925.

7. Reuss, A.: Biologie und Pathologie des Weibes, Berlin, Urban & Schwarzenberg, 1927, vol. 8, pt. 2, p. 729.

Patient's Course.—The condition of the child at birth was poor, and it was immediately taken to the station for premature infants at Michael Reese Hospital. Some cyanosis was noted on admission, but there was a strong, spontaneous cry. The infant was placed in an oxygen bed, and no feedings were given. Ten hours after admission (slightly less than twelve hours after birth) the child died suddenly. Administration of stimulants was of no avail.

Postmortem Examination.—The body was that of a well developed infant Negro girl, weighing 1,350 Gm. and measuring 41 cm. in length. There were no cutaneous lesions, congenital abnormalities or superficial lymphadenopathy.

The abdominal and pleural cavities were lined with smooth, glistening membranes and contained no free fluid. The two leaves of the pericardium were firmly adherent to each other, there being no evidence of a pericardial cavity. Several fine fibrous adhesions extended from the external surface of the pericardium to the mediastinal pleura on both sides. The heart was of average size and usual shape. The external surface was formed by the fibrous pericardium, which presented a dull, ragged appearance. The diaphragm was firmly adherent to the pericardium along both the acute and the obtuse margin and along the entire posterior wall of the heart, including the inferior portions of the auricles. The endocardium and valves presented no gross changes. The myocardium was pale and reddish brown throughout. The foramen ovale and the ductus arteriosus were patent. The aorta and the pulmonary arteries showed no gross changes.

The lungs were of average size. Their external surfaces were pinkish gray, smooth and glistening. All the lobes were firm, and on section the surfaces were smooth and moderately moist. The trachea, larger bronchi and tracheobronchial lymph nodes showed no gross changes. The abdominal viscera and cranial contents were not remarkable.

Microscopic Examination.—Microscopic examination showed that the parietal and the visceral pericardial surfaces were so closely united that the boundary line between the two could not be ascertained. There was no evidence in any of the sections of a pericardial cavity. The two layers formed a thick covering for the myocardium and were composed of dense connective tissue in the outer portions, which was relatively avascular and acellular, while those portions adjacent to the myocardium contained numerous, small, dilated blood vessels and lymphatics and many cellular elements (figure). Most of the cells were lymphocytes, although an occasional polymorphonuclear leukocyte was also encountered. These cells were scattered or arranged in small or large aggregations and often were found in the connective tissue septums which penetrated into the myocardium from the pericardium. Some of the larger veins in the pericardium contained recent thrombi. The myocardium itself showed no histologic changes. Several small subendocardial hemorrhages were seen. In sections taken from the anterior wall of the heart, a hemolymph gland from the anterior portion of the mediastinum was observed to be closely attached to the fibrous pericardium at the base of the heart. Sections taken from the left ventricle, near the apex, showed that the myocardium was connected with the diaphragm by means of a dense layer of connective and fibrous tissue, which was infiltrated in the portions adjacent to the myocardium with lymphocytes and occasional polymorphonuclear leukocytes. No pericardial cavity was present.

The lungs showed evidence of a peculiar recent pneumonia and the presence of giant cells. These changes, obviously not related to the old pericarditis, will be discussed in another paper.

The liver showed persistence of hemopoietic foci in the sinusoids and in the periportal and subcapsular connective tissue. The pancreas showed definite increase in the interlobular and intralobular connective tissue, which was infiltrated with lymphocytes and a smaller number of plasma cells and polymorphonuclear leukocytes.

Sections taken through the lower portion of the femur showed no evidence of chondroepiphysitis. Histologic examination of other tissues showed no evidence of pathologic changes.

Extensive search for spirochetes with use of Kanzler's modification of the Levaditi method in sections from the heart, the lungs, the liver and the pancreas gave negative results. Gram-Weigert, Ziehl-Neelsen and Giemsa preparations also showed no bacteria.

Section of the myocardium and adjacent pericardium. Note the new formation of blood vessels and the marked lymphocytic infiltration. Iron hematoxylin–eosin stain; × 75.

COMMENT

In seeking an explanation for the pericarditis, the following facts must be considered. The mother definitely had syphilis, and she received no antisyphilitic therapy until the sixth month of her pregnancy. The only pathologic changes observed in the child that perhaps can be definitely ascribed to syphilis were those in the pancreas. Though spirochetes were not found in the tissues, it must be realized that even in the tissues of children born with more pronounced syphilitic changes spirochetes are often not demonstrable. Furthermore, the therapy that the mother received may well have caused the destruction of these organisms. The presence of so many lymphocytes in the pericardial regions, also, is compatible with syphilitic changes.

In the case cited by Reuss, the mother gave a history of two attacks of influenza during the pregnancy, and her child, also, showed definite syphilitic changes. In Homolle's case, the mother died of a purulent infection. In these 2 cases, the "influenza" of the one mother and the purulent infection of the other during pregnancy may have been the cause of the fetal pericarditis. In the case here reported there was no history of any infection during the pregnancy. Whether syphilis was responsible for the production of the pericarditis cannot be answered definitely, although it seems most likely.

SUMMARY

An instance of fetal pericarditis is reported in a newborn infant. Only 7 similar cases were found in the literature. The mother of the child had syphilis and received antisyphilitic treatment, which was started in the sixth month of her pregnancy. The possibility of a syphilitic origin of the pericarditis is discussed.

DEFECTIVE PERICARDIAL SAC AND INTERATRIAL SEPTUM AND ATRESIA OF PULMONIC ORIFICE

RUDOLF OSGOOD, M.D.
AND
BENJAMIN SPECTOR, M.D.
BOSTON

The following case is reported because of the presence of two rare anomalies in the same heart, namely, defective pericardial sac and unusually extensive defects of the atrial septum. In addition, there were other defects of the heart, as well as anomalies of other viscera, indicative of additional abnormalities in embryonic development.

In a recent article by Patten,[1] which includes an excellent bibliography, various developmental defects at the foramen ovale are described and embryologic interpretations of them made. Up to 1936, 68 cases of deficient pericardial sac had been reported in the literature.[2] The degree of deficiency varied from small circular defects of the sac to its complete absence. Much has been written on the embryologic explanation of this anomaly. It is generally agreed that it represents a patent pleuropericardial foramen resulting from a disturbance in the development of the celomic cavities and the pleuropericardial membrane.[3]

REPORT OF A CASE

Clinical History.—The patient's mother was a primipara; the pregnancy followed a normal course, and the labor, which was not difficult, lasted twelve hours and forty-nine minutes. Presentation was right occipitoposterior. Fetal heart sounds were not made out at the onset of labor, and after delivery no heart beat was perceptible. The infant gasped a few times and died. The mother made an uneventful recovery. The family history was irrelevant. There was 1 other child, who died in infancy of "intestinal influenza."

Postmortem Examination.—The body was that of a well developed and well nourished, white male infant, weighing 6 pounds (2,722 Gm.). There were no external congenital anomalies or skeletal deformities. The skin was pale, non-

From the Departments of Pathology and Anatomy, Tufts College Medical School, and the Evangeline Booth Hospital.

1. Patten, B. M.: Developmental Defects at the Foramen Ovale, Am. J. Path. **14**:135-161, 1938.

2. Ladd, W. E.: Congenital Absence of Pericardium, New England J. Med. **214**:183-187, 1936.

3. Moore, R. L.: Congenital Deficiency of the Pericardium, Arch. Surg. **11**: 765-777 (Nov.) 1925. McGarry, R. A.: A Case of Patency of the Pericardium and Its Embryological Significance, Anat. Rec. **8**:43-54, 1914. Keith, A.: The Hunterian Lectures on Malformations of the Heart, Lancet **2**:359-363, 433-435 and 519-523, 1909.

icteric and devoid of petechiae. There was edema of the scalp and scrotum. The head was of normal size and shape and was symmetric. The anterior and posterior fontanels were unusually large and were continuous with one another, so that no true sagittal suture was present. The combined length of the fontanels was 13.5 cm., and the width of the anterior fontanel was 5.5 cm. The ears, eyes and nasal passages were normal. There was one defective, loose, lower incisor. No swellings were visible in the neck. The thoracic cage was symmetric and of normal size. The abdomen was symmetric, and its anterior surface was at a slightly lower level than that of the chest. The testes were descended. There was no superficial lymphadenopathy. The extremities were not remarkable.

Peritoneal Cavity: Examination of the peritoneal cavity revealed the following noteworthy features: There was about 25 cc. of thin, clear, amber fluid present. The diaphragm, instead of assuming the normal domelike position with the concave

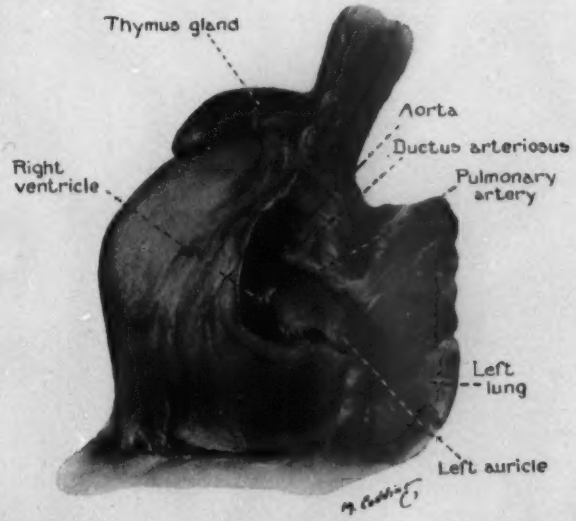


Fig. 1.—External appearance of the pericardial sac as seen from the left lateral aspect, showing the pericardial defect and its relation to the aorta, the pulmonary artery, the ductus arteriosus, the left auricle and the left lung, which is small and compressed lateroposteriorly. The right lung lies completely behind the pericardial sac.

surfaces upward, presented a downward convexity and bulged conspicuously into the upper portion of the peritoneal cavity, as though a large intrathoracic mass was present. As a result of the depression of the diaphragm, there was a general downward displacement of all the viscera in the peritoneal cavity, and the liver was unusually exposed and conspicuous. The spleen was two to three times normal size. The kidneys were slightly enlarged and polycystic and were displaced about 1 cm. downward. There was slight retroperitoneal edema. On cutting of the umbilical vein, unusually profuse and prolonged bleeding occurred, with escape of about 75 cc. of blood.

Thoracic Cavity: The thoracic cavity was nearly completely filled by a huge pericardial sac that overlay and totally obscured from view the underdeveloped lungs, which were compressed posteriorly. The transverse diameter of the peri-

cardial sac was 8 cm. (the measurement was taken after the escape of considerable blood from the heart via the liver following transection of the umbilical vein). The transverse diameter of the thoracic cavity at its widest part was 10 cm. The cephalocaudad dimension of the pericardial sac was 7.5 cm. In the left pleural cavity there was about 5 cc. of thin, clear, amber liquid, such as is normally found in the pericardial sac. The right pleural cavity was free from liquid. The lungs possessed the usual number and arrangement of lobes, but they were one-half or less the normal size and lay entirely behind the large pericardial sac. The thymus was of average size and shape.

Pericardial Sac and Heart: In the upper left quadrant of the pericardial sac was a circular defect, 3 cm. in diameter, that communicated with the left pleural cavity and through which most of the left auricular appendage of the heart protruded. The left lateral border of this pericardial defect was attached to and reflected from the ascending aorta, the pulmonary artery, the lateral aspect of the base of the left auricular appendage and the hilus of the left lung. Elsewhere the edge of the defect was unattached. Since practically all of the blood within

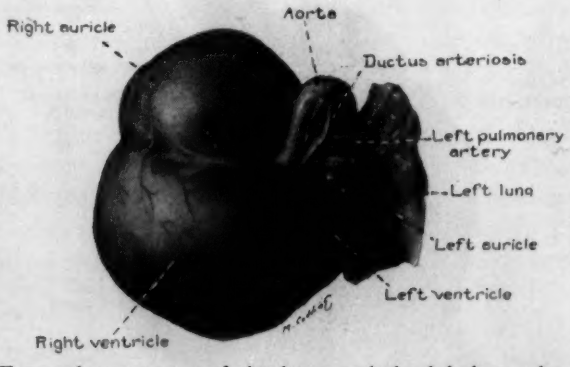


Fig. 2.—External appearance of the heart and the left lung after delivery of the heart through the pericardial defect, showing the relations and the relative sizes of the auricles, the ventricles, the vessels and the left lung.

the heart had escaped by the time that organ was examined, it was possible to extricate the entire heart through the pericardial defect, without injury to the pericardium. The right auricle and ventricle comprised the greater portion of the heart, while the left ventricle, small and thick walled, appeared as a relatively firm, diminutive appendage fused to the huge, flabby, thin-walled right ventricle. The left auricle was small but proportionate in size to the left ventricle. Both of the left chambers, although small compared with the total size of the heart, were slightly larger than normal for a child of this age. The capacity of the right auricle was estimated as about 75 cc., and that of the right ventricle, about 100 cc.

The heart was opened by an incision passing down the right lateral border of the right atrium and ventricle and by a similar incision passing down the left lateral border of the left auricle and ventricle. Adequate exposure of the cardiac chambers was thus obtained. Examination of the interior of the heart and the associated vessels disclosed the following conditions: The superior and the inferior vena cava entered the dilated, thin-walled right atrium in relatively normal positions. The pulmonary veins entered the left auricle in the usual manner. The tricuspid

ring was widely dilated and incompetent. The tricuspid leaflets, especially the medial, were defective and ill defined. They averaged 2 cm. in width; they were thin and transparent and were in part attached to the endocardium of the ventricle. The chordae tendineae were only a few millimeters in length, and they inserted into the trabeculae carneae. There were no distinct papillary muscles. A deep red, oval, firm, mulberry-shaped cavernous hemangioma, 4 by 8 mm. in greatest diameter, was attached to the base of the tricuspid valve and the adjacent posterior wall of the right ventricle, close to the interventricular septum. The pulmonic cusps and orifice were lacking. A small dimple marked the site of the atretic pulmonic valve. The pulmonary artery, while completely atretic at its origin, had a small patent lumen, 1 to 2 mm. in diameter, just distal to the atresia, and gave origin to patent right and left branches. The latter were easily followed to the hili of the lungs by means of a 1 mm. probe.

There was a large round orifice, 1.5 cm. in diameter, situated just above the aortic leaflet of the mitral valve and above the tricuspid ring, which allowed free

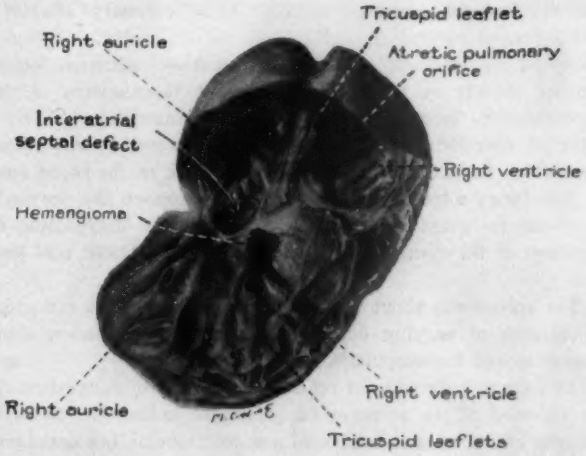


Fig. 3.—The right auricle and ventricle laid open to show the interatrial defect, the position of the atretic pulmonary orifice and the tricuspid leaflet with the hemangioma. The left auricle and ventricle lie entirely behind the upper half of the figure.

communication beween the right and left atria. There was no evidence of a septum primum. There was, however, a thin fold of fibrous tissue representing the fused left valve of the sinus venosus and the septum secundum. This fold was 10 mm. in length, projected 5 mm. into the atrium from its posterosuperior aspect, was directed caudad toward the region of the coronary sinus and the atrioventricular opening and was the only structure found that could be interpreted as a septal membrane. On the basis of anatomic landmarks, one of the following possibilities may explain the interatrial defect: complete failure of development of the septum primum and only partial development of the septum secundum or complete resorption of the septum primum, which had once developed, and incomplete development of the septum secundum. We are inclined to agree with Patten's opinion, expressed in 1931 [4] and 1938,[1] about similar defects seen in his own

4. Patten, B. M.: The Closure of the Foramen Ovale, Am. J. Anat. **48**:19-44, 1931.

material, namely, that the condition "points strongly toward secondary absorption of a once present septum primum." The remains of the right valve of the sinus venosus were evident in the distinct preservation of the crista terminalis and the respective valves of the inferior vena cava and the coronary sinus.

There was no stenosis or atresia of the mitral and aortic valves, and their cusps were normal in number and position. The papillary muscles and chordae tendineae of the left ventricle were distinct and well developed. The interventricular septum was intact. There was no coarctation of the aorta. The ductus arteriosus was patent and of average size. The measurements of the heart after fixation in a dilute solution of formaldehyde U. S. P. (1:10) were: tricuspid valve, 10.5 cm.; mitral valve, 3.5 cm.; thickness of right ventricle, 0.1 cm. or less; thickness of left ventricle, 0.3 to 0.5 cm.; length of right ventricle from base to apex, 3.2 cm., and width from right lateral border to interventricular septum, 6 cm.; length of left ventricle from base to apex, 2.5 cm., and width from left lateral border to interventricular septum, 2 cm. (outside measurements). The aortic valve was not laid open but was sufficiently exposed for one to see that its size and development appeared normal. The coronary arteries originated normally and appeared normal.

There was no evidence of cardiac inflammation, scarring, hemorrhage or infarction, either grossly or microscopically. The hemangioma of the tricuspid valve was composed of large, dilated, thin-walled sinusoidal channels lined by a flattened layer of endothelial cells with a small amount of underlying acellular fibrous tissue, which formed the supporting framework of the blood spaces.

Lungs: The lungs were underdeveloped and possessed the normal number of lobes. There was no gross evidence of inflammation. Microscopic examination showed aspiration of the contents of the amniotic sac. There was no fibrosis or inflammation.

Spleen: The spleen was about three times normal size, dark red and firm and it had several fissures of varying depth. Microscopic examination showed diffuse fibrosis, congestion and hematopoiesis.

Liver: The liver grossly was not remarkable except for congestion. Microscopic examination revealed slight increase of periportal connective tissue, congestion, dilatation of lymphatics, minute periportal and intralobular hemorrhages and a few foci of hematopoiesis.

Gallbladder and extrahepatic biliary passages: These structures were normal.

Pancreas: The pancreas was not remarkable grossly but showed microscopic evidence of slight immaturity and hematopoiesis in the stroma.

Alimentary Tract: This structure was normal.

Kidneys: The kidneys were of similar size, shape and general gross appearance. They measured 3.8 cm. from pole to pole and were studded with numerous cysts of varying sizes, ranging up to 7 mm. in diameter, which gave to their surface an uneven, nodular appearance. The majority of the cysts were about 3 to 4 mm. in diameter. Coronal sections through the kidneys revealed a relatively small amount of red parenchyma interspersed and distorted by many cysts. The calices and pelves were encroached on and obscured by the cysts of the parenchyma. The ureters were not unusual. The microscopic picture was essentially that of polycystic kidneys. The cysts were lined by a row of simple cuboidal epithelial cells and were surrounded by distorted parenchyma, much of which appeared otherwise well preserved. The stroma was edematous. There were many scattered hemorrhages involving the stroma and the tubules. Foci of hematopoiesis were present in the medullary stroma.

Adrenal Glands: The adrenal glands were compressed and flattened. Microscopic sections showed no significant changes.

Thyroid Gland and Thymus: These glands were normal except for congestion and petechial hemorrhages.

Testes: The testes were grossly normal. Microscopic examination showed edema, congestion and petechial hemorrhages in the stroma.

Brain and Spinal Cord: These structures were grossly normal.

SUMMARY

The anatomic observations in an unusual case of anomalous development of the heart are reported, of which the outstanding embryologic defects were: defective pericardial sac, large interatrial communication and atresia of the pulmonary artery at its origin. The last condition was responsible for extreme dilatation of the right atrium and ventricle and marked stretching and incompetence of the tricuspid valve. A hemangioma was attached to the tricuspid valve.

Explanations of the pericardial and atrial defects are briefly indicated.

KARTAGENER'S TRIAD

SITUS INVERSUS VISCERUM, BRONCHIECTASIS AND PARANASAL SINUSITIS

S. A. ADLAND, M.D.
AND
ROBERT A. J. EINSTEIN, M.D.
DENVER

Adams and Churchill [1] recently reviewed the literature and reported 5 cases in which the Kartagener triad of situs inversus viscerum totalis, bronchiectasis and sinusitis was exhibited. Glaum,[2] in 1938, and Ingraham,[3] Rosenthal [4] and Becker,[5] in 1939, reported additional cases in which these abnormalities were associated, thus bringing the total number reported to 27. In many of the cases the congenital origin of the bronchiectasis was not supported by definite clinical evidence, and in many the acquired nature of the bronchial disease could be definitely established.[5a] Several investigators, including Kartagener [6] and Vernli-Haessig,[7] supported the contention of Sauerbruch that in about 80 per cent of the cases of bronchiectasis occurring in childhood the origin is congenital. What role the transposition of the heart plays in the development of bronchiectasis is not clearly known, nevertheless, the exceed-

From the Medical Department of the National Jewish Hospital, Charles J. Kaufman, M.D., Medical Director.

1. Adams, R., and Churchill, E. D.: Situs Inversus, Sinusitis and Bronchiectasis: Report of Five Cases, J. Thoracic Surg. **7**:206-217, 1937.

2. Glaum, K.: Congenital Bronchiectasis with Situs Viscerum Inversus, Beitr. z. Klin. d. Tuberk. **91**:422-426, 1938.

3. Ingraham, R.: Case of Situs Inversus with Extensive Bilateral Bronchiectasis Dating from Early Childhood, M. Women's J. **46**:140-145, 1939.

4. Rosenthal, D. B.: Case of Bronchiectasis with Visceral Transposition, M. J. Australia **1**:761-764, 1939.

5. Becker, B.: Case of Situs Inversus Viscerum Totalis with Congenital Bronchiectasis, Beitr. z. Klin. d. Tuberk. **94**:73-75, 1939.

5a. Nuessel, E. K., and Hellbach, H.: Bronchiectasis in Situs Inversus Viscerum Totalis, Beitr. z. Klin. d. Tuberk. **84**:424-428, 1934.

6. (*a*) Kartagener, M.: Pathogenesis of Bronchiectasis with Lateral Transposition of Viscera: Four Cases, Beitr. z. Klin. d. Tuberk. **83**:489-501, 1933. (*b*) Kartagener, M., and Horlacher, A.: Bronchiectasis in Situs Viscerum Inversus, Schweiz. med. Wchnschr. **65**:782-784, 1935; (*c*) Situs Inversus Totalis and Nasal Polyposis in Case of Familial Bronchiectasis: Pathogenesis of Bronchiectasis, Beitr. z. Klin. d. Tuberk. **87**:331-333, 1935.

7. Vernli-Haessig, A.: Situs Inversus with Congenital Bronchiectasis: Case Report, Ztschr. f. Tuberk. **77**:120-122, 1937.

ingly high incidence of bronchiectasis when such an anomaly is present is noteworthy. It cannot be stated with any degree of certainty whether there is associated bronchial maldevelopment or whether the disease is coincidental and related to the lowered general resistance in cases of the cardiac anomaly, as suggested by Kartagener.[6]

In view of the continued uncertainty about the relation of congenital anomalous development to the occurrence of bronchiectasis, we wish to report the following case in which there were situs inversus viscerum totalis, bronchiectasis and paranasal sinusitis, in the hope that additional light may be thrown on this perplexing problem.

REPORT OF A CASE

History.—M. R., a girl born on July 20, 1925, was admitted to the children's division of the National Jewish Hospital on March 7, 1936 because of cough and expectoration of purulent material, which had been present almost continuously since 1928. There was a history of frequent colds from birth. At 1 month of age the child had had pneumonia, which was followed by other attacks of pneumonia at 1, 3, 7 and 8 years of age and by an attack of lobar pneumonia in 1935. Tonsillectomy had been scheduled for September 1930, but this had been postponed because of persistent rales in the upper part of the right side of the chest. In July 1931 bilateral otitis media and acute tonsillitis developed. Examination of the chest in 1930 had revealed transposition of the thoracic organs and increased fibrosis extending along the bronchi into each lung with a few small areas of mottling opposite the hilus of the left lung.

First Hospitalization.—On Jan. 31, 1933 she had been hospitalized because of bilateral maxillary sinusitis, and physical examination at that time had revealed crackling rales distributed diffusely over the chest, most marked on the left side anteriorly. On March 11, 1933 tonsillectomy, adenoidectomy and puncture of the maxillary sinuses had been performed. Thick pus had been liberated from the sinuses. A roentgenogram of the chest taken on Feb. 4, 1933 had revealed a marked increase of the infiltration in the hilus and also in the peribronchial region. Roentgen studies of the paranasal sinuses had shown marked clouding of the ethmoid sinuses and antrums on both sides. On discharge, on April 15, 1933, from the Children's Hospital, where the operation was performed, the following diagnoses had been made: (1) situs inversus viscerum totalis, (2) bronchiectasis, (3) chronic maxillary sinusitis and (4) chronic tonsillitis and adenoiditis.

Course.—Between 1933 and 1936 the amount of thick, mucopurulent sputum expectorated daily increased to 1 or 1½ ounces (30 to 45 cc.), and the patient continued to have a thick, purulent nasal discharge.

Second Hospitalization.—On admission to the National Jewish Hospital, she complained of a loose, hacking cough, increase of temperature to 99.2 F. and pain in the anterolateral aspect of the chest on the left side. Examination of the lungs revealed crepitant rales throughout anteriorly, including the apexes, on quiet breathing. These were increased after cough. Numerous wheezes and other adventitious sounds were heard throughout. Posteriorly, coarse rales were heard from the sixth dorsal vertebral spine to the base of the lung. The apical impulse of the heart was found in the fifth interspace on the right side. Bronchiographic studies revealed cylindric dilatations in the lower lobe of the left lung and also in the middle and lower lobes of the right lung. Barium studies of the gastro-

intestinal tract showed situs inversus of all the intra-abdominal viscera. A roentgenogram of the chest revealed typical dextrocardia, the heart being of normal size and the left side of the diaphragm being higher than the right. All leads were reversed in the electrocardiogram. Roentgen examination of the paranasal sinuses showed that the antrums and the left ethmoid sinuses were dense and that the right ethmoid sinuses and both sphenoid sinuses were clouded. Tuberculin tests were frequently repeated during her residence in the hospital; the reaction was persistently negative to 1 mg. of old tuberculin administered intracutaneously. The total white cell count persistently ranged from 12,200 to 27,300 and the neutrophils from 37 to 85 per cent, including 4 to 9 per cent immature cells. The results of frequent examinations of the sputum by direct smear, culture and inoculation of guinea pigs were negative for tubercle bacilli. Cultures of the sputum for pyogenic organisms revealed gram-positive cocci, and those for fungi resulted in the growth of Aspergillus. No elastic fibers were found in the sputum.

Course.—On Nov. 22, 1937 a second adenoidectomy was performed because of the child's consistent mouth breathing, postnasal discharge and frequent colds. A few tonsillar tags also were removed. An attempt to drain the right antrum at that time was unsuccessful. Little relief was brought about by the operation. Postural drainage three times daily was instituted and resulted in the expectoration of 2 ounces (60 cc.) of purulent material at first; later the amount decreased to 1 to 1½ ounces (30 to 45 cc.). Cough persisted throughout her residence in the hospital. Examination of the chest revealed the constant presence of bronchial breath sounds over the base of the left lung anteriorly and numerous crepitant rales over the lower two thirds of the same lung. On the right side there were numerous coarse crepitant rales over the base of the lung posteriorly. Periodically, at two to three month intervals, she experienced elevations of temperature to 100 or 101 F., which subsided after several days. Gain in weight was steady; however, it was gradual, and she always stayed well below the standard weight. She was discharged to her home on Aug. 22, 1939. Her condition was considered quiescent.

Diagnosis.—The final diagnoses were: (1) bronchiectasis; (2) chronic rhinitis; (3) dextrocardia, with situs inversus; (4) malnutrition, and (5) poor posture.

SUMMARY AND CONCLUSIONS

A case is reported in which there were situs inversus viscerum totalis, bronchiectasis and paranasal sinusitis, the triad of symptoms first described by Kartagener.

In view of the rareness of situs inversus viscerum totalis, which is not infrequently accompanied by other congenital anomalies, the high incidence of bronchiectasis in patients who have complete transposition of the viscera supports the hypothesis that this type of bronchiectasis is of congenital origin.

We believe that the infection of the upper respiratory tract in the case reported was not primary, although it may have played a part in subsequently aggravating the underlying bronchial disease.

CONGENITAL ABSENCE OF THE FIBULA

ITS OCCURRENCE IN A PREMATURE NEGRO INFANT

ROLAND B. SCOTT, M.D.
WASHINGTON, D. C.

The pediatric literature contains only scanty references to a fairly common deformity of the lower extremity usually referred to as congenital absence of the fibula. Lapasset and Cahuzac[1] in 1935 found 295 cases reported in the literature. At present, over 300 cases have been recorded; however, most of these reports have appeared in the orthopedic literature.

Herron and Sanford[2] have called attention to the fact that the condition has not received sufficient recognition from the pediatric point of view. Certain physical signs characteristic of the anomaly make its recognition in a newborn child fairly easy. It is incumbent on the pediatrician who first observes the infant after birth to diagnose the condition and to make the appropriate recommendations for its subsequent treatment.

REPORT OF A CASE

C. G., a Negro girl, was born prematurely, weighing at birth 3 pounds 5 ounces (1,500 Gm.). Delivery was spontaneous, and the baby was in no distress. The parents were young and apparently in good health. There was no history of familial anomalies of the extremities. The results of the Wassermann and Kahn tests were negative for the infant and the parents.

Physical examination (fig. 1) revealed a premature baby who was normal except for a deformity of the left lower extremity. This member was 2 cm. shorter than its fellow. The left leg and foot were smaller in circumference and shorter than the corresponding parts on the right side. The left leg was bowed into a forward convexity, causing slight angulation at its middle third. The skin was normal at the site of greatest angulation. On palpation neither the fibula nor the external malleolus could be outlined on the left side. The ankle joint was relaxed, and the foot was in equinovalgus position. All of the digits were present and appeared normal.

Roentgenograms (fig. 2) showed slight anterior bowing of the left tibia, which appeared slightly thicker than the right. Measurement by means of a teleroentgenogram showed the left tibia to be 0.7 cm. shorter than the right. The left fibula was absent. The distal femoral epiphysis was visualized as a minute shadow on the right side, but was not seen on the left. Both proximal tibial

From the Department of Pediatrics, Provident Hospital, Chicago.

1. Lapasset and Cahuzac: Absence congénitale du péroné, Rev. d'orthop. **22**:110, 1935.

2. Herron, P. H., and Sanford, H. N.: Congenital Absence of the Fibula, J. Pediat. **2**:454, 1933.

centers of ossification were absent. There were three tarsal centers of ossification at the right ankle, but only a small solitary center, apparently for the calcaneus, appeared on the left side.

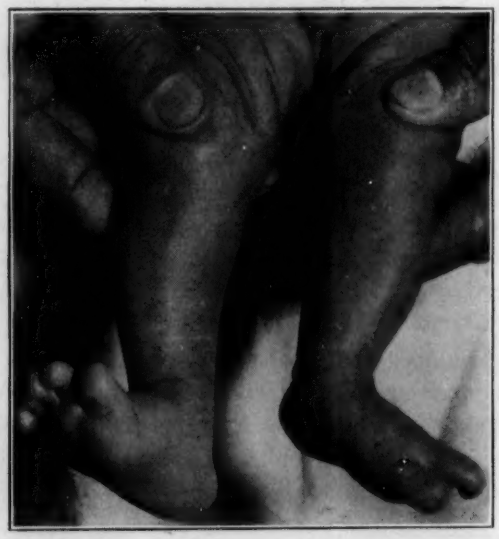


Fig. 1.—Photograph showing the slight anterior bowing of the left leg, which is shorter and smaller than the right, the relaxed left ankle joint and the left foot held in equinovalgus position. The right lower extremity is normal.

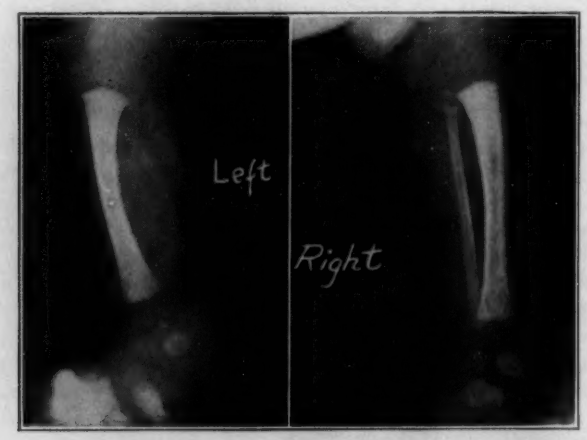


Fig. 2.—Roentgenogram showing the absence of the left fibula and the shortening and anterior bowing of the left tibia. There is only one tarsal center of ossification at the left ankle, while there are three centers at the right ankle.

A plaster cast was applied to the left leg and foot before the baby was released from the nursery. When last seen, during her sixth months of life, the

infant was in good nutrition, weighing 14½ pounds (6,568.5 Gm.). There was, however, little change in the deformity of the left lower extremity.

PATHOGENESIS

There is no unanimity of opinion regarding the primary cause of this syndrome. Heredity seems to have been a factor in only a few isolated cases. Volkmann [3] described a hereditary congenital deformity of the ankle joint affecting several members of a family. The theory of external traumatism resulting in fracture and deformity of the tibia and resorption of the fibula during the fetal period appears untenable in most instances. The hereditary element was absent in the case described here, and there was no history of external violence.

Some writers have attributed the entire syndrome, including the absence of the fibula, the associated deformity of the tibia and the dimple in the skin over the bend in the tibia, to pressure from hypothetic adhesions or a too tightly fitting amnion. This presumed pressure is thought to interfere with the blood supply and innervation, thereby causing hypoplasia or dwarfing of the affected parts. However, since embryonic development demands that the defect be manifest as early as the sixth week of fetal life, the theory of congenital amniotic adhesions and bands is unlikely.

The most tenable explanation regarding the pathogenesis of the deformity is the one suggested by Freund,[4] Harmon and Fahey [5] and others, namely, a defect in the germ plasm or anlage which is transmitted as a recessive character. The congenital shortness of the leg, as well as the hypoplastic condition of the tibia and the tarsal epiphysial centers of ossification in the affected limb, all points toward an early intrinsic disturbance in growth of the extremity. The demonstration of the dwarfing or hypoplasia of the affected limb in the newborn infant practically eliminates atrophy of disuse (lack of weight bearing) as an etiologic factor.

The associated deformity of the tibia, that is, the shortening, thickening and bending, has been attributed by Freund [4] to both a faulty primary anlage for the skeleton and musculature and a disturbance in the balance of growth in length between the muscles of the calf and the tibia itself. He has expressed the belief that the muscles share in the immature development of the affected limb.

---

3. Volkmann, R.: Ein Fall von hereditärer kongenitaler Luxation beider Sprunggelenke, Deutsche Ztschr. f. Chir. **2**:538, 1873.

4. Freund, E.: Congenital Defects of Femur, Fibula and Tibia, Arch. Surg. **33**:349 (Sept.) 1936.

5. Harmon, P. H., and Fahey, J. J.: The Syndrome of Congenital Absence of the Fibula, Surg., Gynec. & Obst. **64**:876, 1937.

If the muscles of the calf fail to grow in length at the same rate as the tibia, they will form a tight string on this bone. The highly plastic material of the fetal tibia will have to adapt itself to the shortness of the muscles of the calf either by an anterior bowing or by decreased growth in length or by both. In either instance the process leads to a lack of maturation of the tibia, which preserves its embryonal form. This disproportion in length between the tibia and the muscles of the calf accounts for the tight achilles tendon and the equinus position of the foot. If the bending of the tibia is marked, the bone may become adherent to the overlying skin at the point of greatest convexity, with the result that a dimple is formed at the site of contact.

Bagg [6] has shown by a series of interesting experiments that injury to the germ plasm even before mating may lead to congenital deformity. He was able to produce certain deformities of the feet in mice by light doses of roentgen rays. The descendants of these animals so treated showed a high percentage of abnormalities of the limbs expressed mainly as syndactylism, hypodactylism, polydactylism, clubfoot and congenital amputations. By selective mating he was able to increase the incidence of foot defects. He found that the anomalies were transmitted as a mendelian recessive character. Embryologic studies showed that the earliest foot defect was associated with the formation of a blister-like bleb which raised the epithelium of the foot, usually in a localized area, followed by the escape of blood into the bleb and the formation of a localized blood clot. The extent of the pathologic process and its anatomic location determined whether the later developing foot was to show clubbing, hypodactylism, syndactylism or congenital amputation. This work of Bagg appears to support the view that the syndrome of congenital absence of the fibula has its origin in an intrinsic defect in the germ plasm which is expressed in terms of a localized arrest in embryonic development.

With regard to the race and prematurity of the infant whose case is described here, the statistics of Murphy [7] are of interest. In a study of 890 instances of congenital malformation, he found the incidence to be nearly twice as high in the white as in the Negro race (ratio 57 to 32). He also observed [8] that premature births occurred among the malformed subjects more than four times as often as among the normal siblings. (ratio 18.3 to 4). Congenital anomalies apparently occur with greater frequency among prematurely born children than among those born at full term.

---

6. Bagg, H. J.: Hereditary Abnormalities of the Limbs: Their Origin and Transmission, Am. J. Anat. **43**:167, 1929.

7. Murphy, D. P.: Congenital Malformation, Philadelphia, University of Pennsylvania Press, 1940, p. 15.

8. Murphy,[7] p. 31.

COMMENT

In man [9] the fibula is a rudimentary bone and bears none of the weight of the trunk, but is of importance on account of its muscular attachments and its participation in the formation of the ankle joint.

Bardeen and Lewis [10] observed that the skeletal mass in the lower limb becomes differentiated into femur, tibia and fibula as early as the sixth fetal week. During the seventh fetal week the rudiments of all the bones of the lower extremity are present in the form of cartilage except the terminal phalanges of the three outer toes. Also at this period all of the muscles of the lower limb except the lumbricales of the foot are distinguishable. By birth the shaft of the fibula is completely ossified, though the ends are still cartilaginous. This early embryonic development of the fibula implies a corresponding early origin of the defect under discussion in this report.

Although most of the papers on this defect have appeared under the title of congenital absence of the fibula, a review of the published material discloses the fact that absence of the fibula is only a part of the complete syndrome. The affected extremity usually shows several congenital defects, which constitute a fairly characteristic and typical picture. These defects may be briefly summarized as follows:

1. There are shortening, dwarfing and anterior bowing of the affected leg, sometimes associated with the presence of a cutaneous dimple or scar over the convexity of the curve. If the bony defect is bilateral, these dimples are usually symmetrically placed.

2. The external malleolus is absent, which allows lateral and posterior dislocation or relaxation of the ankle joint.

3. The foot is commonly held in equinovalgus position.

4. The achilles tendon is shortened.

5. The toes are often absent, webbed or hypoplastic.

6. Associated anomalies are often present elsewhere in the body.

7. Roentenograms reveal: (*a*) incomplete development or complete absence of the fibula; (*b*) shortening, anterior bowing and thickening of the tibia on the affected side; (*c*) absence, delay in appearance or fusion of certain tarsal and metatarsal centers of ossification, and (*d*) delay in appearance of the proximal and distal tibial epiphyses on the affected side.

In the case reported here most of the defects outlined were present. The cutaneous dimple or pseudoscar sometimes found over the convexity

9. Morris, H.: Human Anatomy, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1933, p. 249.

10. Bardeen, C. R., and Lewis, W. H.: Development of the Limbs, Body-Wall and Back in Man, Am. J. Anat. **1**:1, 1901.

of the bend in the tibia was absent however. Gaenslen [11] has observed that these scars are found with the greatest frequency in cases in which the angulation in the tibia is sharp and are often absent when there is but slight bending. The digits were all present. The bilateral absence of the proximal tibial centers of ossification may be attributed to the prematurity of the infant. The presence of a single small tarsal center of ossification at the defective ankle, however, reflects the epiphysial retardation that usually accompanies congenital absence of the fibula.

These defects of the fibula are usually classified as total or partial, unilateral or bilateral. The distribution of the 213 cases collected by Nutt [12] was as follows: total unilateral absence, 108; total bilateral absence, 42; partial unilateral absence, 47; partial bilateral absence, 9, and total absence on one side and partial absence on the other, 1. Specific information was lacking in 6 cases.

Freund [4] has proposed the classification of (*a*) complete absence, (*b*) partial absence and (*c*) hypoplasia of the fibula. In the last type both the epiphyses and the diaphysis are developed, but the whole bone is hypoplastic and, as a rule, is located along the lower third of the tibia and does not participate in the formation of the ankle joint. In commenting on the fact that over two thirds of the cases reported in the literature are those of "complete absence" of the fibula, Freund stated:

> Most of the cases reported occur in young children who on clinical and roentgenologic examination may show total absence of the fibula but who a few years later may present a rudimentary fibula in the roentgen picture.

For this reason he cautioned against making the diagnosis of complete absence of the fibula before, at the earliest, the fifth year of life.

The prognosis for good function is generally poor, largely because of the associated deformity of the ankle joint. Corner [13] mentioned 5 patients between the ages of 40 and 70 years to demonstrate that the subjects with congenital absence of the fibula may lead long and useful lives.

Treatment is an orthopedic problem. The obligation of the pediatrician, or the general practitioner, is to establish an early diagnosis and refer the patient for orthopedic care. Treatment should be instituted during infancy, as early use of the limb is necessary to avoid atrophy of disuse. The management varies with the extent of the deformity, the age of the patient and whether the defect is unilateral or bilateral. Treat-

11. Gaenslen, F. J.: Congenital Defects of the Tibia and Fibula, Am. J. Orthop. Surg. **12**:453, 1915.

12. Nutt, J. J.: Congenital Fibular Defects, Surg., Gynec. & Obst. **37**:475, 1923.

13. Corner, E. M.: The Clinical Picture of Congenital Absence of the Fibula, Brit. J. Surg. **1**:203, 1913.

ment is directed at the equinovalgus deformity of the ankle and at the bowing and shortening of the tibia.

Ordinarily, immobilization by a cast and the wearing of corrective shoes are given an initial trial in an effort to aline the foot with the tibia. If this preliminary treatment fails, Harmon [5] has recommended operative lengthening of the posterior and lateral tendons, followed by immobilization in a cast and the use of braces. Constant and early weight bearing is further advised to act as a stimulus to longitudinal growth. Later, the shortening due to the bend in the tibia may be corrected by osteotomy, though in some cases the total shortening may be so great that amputation will be necessary.

SUMMARY

A case of congenital absence of the fibula in a premature infant is reported.

In addition to absence of the fibula this syndrome characteristically consists of: (1) shortening, anterior bowing and dwarfing of the affected leg; (2) shortening and anterior bowing of the tibia; (3) equinovalgus position of the foot, with relaxation of the ankle joint; (4) absence of the external malleolus; (5) absence, delay in appearance or fusion of some tarsal and metatarsal centers of ossification, and (6) absence, webbing or hypoplasia of the toes.

The deformity apparently results from an intrinsic defect in the germ plasm.

The prognosis for good function generally is not very satisfactory.

The diagnosis should be made in the newborn period and an orthopedist consulted about the patient's management before atrophy of disuse appears.

Howard University Medical School.

520 W Street N. W.

RHEUMATIC FEVER IN A NEWBORN INFANT

EDWARD J. DENENHOLZ, M.D.
AND
ALWIN C. RAMBAR, M.D.
CHICAGO

Rheumatic fever during infancy is uncommon, and its occurrence during the newborn period is rare. Gibson,[1] in his chapter "Rheumatic Fever and Chorea," in Brennemann's "Practice of Pediatrics," did not mention it. Wilson [2] has expressed the belief that reports of intrauterine rheumatic fever and rheumatic heart disease are not conclusive. In her clinic, the youngest patient observed for whom the diagnosis of rheumatic fever was confirmed by autopsy was 15 months old. Discussions in recent textbooks likewise attest to the extreme infrequency of this condition. Thus, Holt and Howland [3] stated:

> Rheumatic endocarditis has been reported in newly born infants whose mothers were suffering from active rheumatic fever at the time of birth. Such an event, if it occurs, must be extremely rare; as far as we are aware these cases have not been subjected to critical pathological studies.

Reports in the early pediatric literature concerning rheumatism in the newborn were relatively frequent, though in the past forty years few cases have been recorded. The diagnosis in many of the earlier cases is questionable in the light of present knowledge, since it was made entirely on a clinical basis. It is of interest that since the advent of widespread use of laboratory methods of diagnosis the number of cases reported has greatly diminished. However, in the earlier literature, there were reports of cases under such headings as "acute rheumatism in the newborn" and "rheumatismus neonatorum" in which a diagnosis of sepsis, gonorrheal arthritis or syphilis was unlikely and that of rheumatic fever cannot reasonably be excluded. In most of these, the mother had rheumatic fever before, during or shortly after the time of delivery, which suggests the possibility of intrauterine transmission of the disease.

From the Sarah Morris Hospital for Children, Michael Reese Hospital.

1. Gibson, S.: Rheumatic Fever and Chorea, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 2, chap. 19, p. 1.

2. Wilson, M. G.: Rheumatic Fever, New York, Commonwealth Fund, Division of Publications, 1940, p. 18.

3. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, revised by L. E. Holt Jr. and R. McIntosh, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, p. 1156.

Pocock,[4] in 1882, reported a case of acute rheumatic fever in a newborn infant. Sudden high fever and painful, swollen joints developed in the mother two days before delivery, and twelve hours after birth the same symptoms were evident in the infant. Treatment with sodium salicylate was employed, and the symptoms subsided. Valvular heart disease developed in the mother, but there was no detectable damage to the infant's heart.

In the case reported by Schaefer[5] in 1886 the mother had rheumatic fever five days before delivery. When the baby was 3 days old, it also showed fever and swollen joints, which lasted about two months. The infant was treated with salicylates. No cardiac damage was noted.

In 1888 Guthrie[6] reported a case in which the mother had pain in the abdomen, chills, high fever and polyarthritis three days after delivery. Reddened, swollen joints developed in the baby when it was 10 days old. The symptoms responded to salicylates. No mention is made of the condition of the heart.

In Ferguson's[7] case, reported in 1893, the mother had rheumatic fever, which persisted from the second month of pregnancy until delivery. The baby showed fever and painful joints at birth. Autopsy revealed the heart to be normal.

In Abrahams'[8] case 2, reported in 1897, the mother had acute rheumatic fever, which began during the ninth month of gestation. The mother died three days post partum, and autopsy revealed acute endocarditis. In the infant fever and painful, swollen joints were noted a few hours after birth and a distinct, blowing systolic murmur on the fifth day. The infant recovered in six weeks, though it died at 9 months of age of gastroenteritis. No mention is made of the status of the heart. In Abrahams' case 3 rheumatic fever also developed in the mother after seven months of gestation and acute chorea during the ninth month. Premature birth resulted, the chorea subsiding promptly after delivery. Polyarthritis did not develop in the baby, but it had cyanosis on crying, and "signs of aortic insufficiency" were found, though the day on which they appeared and the nature of these signs were not stated.

A highly interesting case that makes transmission of rheumatic disease through the placenta seem possible was reported by Kissane

---

4. Pocock, F. E.: A Case of Acute Rheumatism Occurring in a Newly Born Infant, Treated with Salicylate of Soda, Lancet **2**:804, 1882.

5. Schaefer: Ein Fall von acutem Gelenkrheumatismus bei einer Mutter und deren neugeborenem Kinde, Berl. klin. Wchnschr. **23**:79, 1886.

6. Guthrie, A.: A Case of Acute Rheumatism in an Infant Eleven Days Old, M. Progress **10**:746, 1888.

7. Ferguson, J. H.: A Case of Intrauterine Rheumatism, Edinburgh Hosp. Rep. **1**:608, 1893.

8. Abrahams, R.: Rheumatismus Neonatorum, M. Rec. **50**:574, 1897.

and Koons [9] in 1933. The mother had active rheumatic fever throughout pregnancy, and the infant was born with red, swollen, painful joints. Thirty minutes after birth, abnormal heart sounds were noted in the infant. At the age of 6 months there was an acute recurrence of rheumatic fever. Heart failure was present at intervals until death occurred at the age of 10 years. Autopsy revealed stenosis of the tricuspid and mitral valves and histologic changes typical of rheumatic heart disease. No evidence of congenital heart disease was found.

The case of polyarthritis reported by Richdorf and Griffith [10] in 1926 has been cited by some authors [11] as an example of rheumatic fever in a newborn child. Fever and polyarthritis developed in a woman three days before delivery. Three days post partum she had a soft systolic murmur at the apex. When her infant was 6 days old he displayed fever and swollen, tender joints. On the thirteenth day, when definite fluctuation was noted in the right knee joint, it was operated on, and thick, yellow, mucoid material was obtained. From this fluid and from the mother's blood Streptococcus viridans was grown in pure culture. The authors expressed the belief that in this case the evidence pointed toward an intrauterine infection of the infant through the placenta by organisms circulating in the mother's blood. From the data given, we believe that this case probably is an example of sepsis with purulent arthritis, rather than of rheumatic fever of the newborn. The striking similarity of this case to those reported by the older writers as examples of rheumatic fever on the basis of clinical observations alone illustrates well the point that some of the earlier cases may have been instances of sepsis or of other conditions.

REPORT OF A CASE

D. S., a white female infant, who had been entirely breast fed, was admitted to Sarah Morris Hospital, to the service of Dr. Jesse Gerstley, at the age of 18 days, with the complaint of fever, irritability and swelling of the joints of eight days' duration. She was born spontaneously at full term after an uneventful pregnancy and a four hour labor. She weighed 3,990 Gm. at birth. When the infant was 7 days old, the mother suddenly showed painful, swollen, tender joints and fever (temperature between 100 and 102 F.) accompanied by profuse sweats. The pain, tenderness and swelling of the joints migrated from the right elbow to the right

9. Kissane, R. W., and Koons, R. A.: Intra-Uterine Rheumatic Heart Disease, Arch. Int. Med. **52**:905 (Dec.) 1933.

10. Richdorf, L. F., and Griffith, W. H.: Polyarthritis: Report of a Case in an Infant Six Days Old, Am. J. Dis. Child. **31**:250 (Feb.) 1926.

11. Griffith, J. P. C., and Mitchell, A. G.: The Diseases of Infants and Children, ed. 2, Philadelphia, W. B. Saunders Company, 1937, p. 733. Swift, H. F., and McEwen, C., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1939, vol. 5, pt. 1, p. 12. Paul, J. R.: Age Susceptibility to Familial Infection in Rheumatic Fever, J. Clin. Investigation **10**:53, 1931.

ankle, back to the right elbow and then to the left ankle. The attending physician made a diagnosis of acute rheumatic fever and administered large doses of salicylates, with which treatment the symptoms promptly subsided. Three days after the onset of the mother's illness, the baby had a slight fever and cried when her right arm was touched. She became irritable, took her feedings poorly, vomited two to three times daily, had profuse sweats and cried when she was picked up or when the bed clothes were disturbed. The temperature varied from 100 to 103 F. After a few days, swelling became evident over both ankles, which were tender and slightly reddened. The swelling then subsided, after which the right wrist became reddened and swollen.

Family History.—The father was living and well. The family lived with the maternal grandfather and grandmother, both of whom were well and had no history of rheumatism.

The mother had had no previous attacks of rheumatism, nor was there a history of chorea or of heart disease. There was no vaginal discharge, foul lochia or evidence of puerperal sepsis. There was no history of venereal disease, and during pregnancy vaginal smears were negative for gonococci and negative

The patient at 18 days of age, showing the swelling of the right wrist and the phalanges of the left hand.

Wassermann and Kahn reactions were obtained. The mother was said to have had a "touch of tuberculosis" a few years before. She had had 1 previous child, delivered at full term, six years before, who had lived only for a few hours. The cause of death was unknown. The mother had not received any serum or foreign protein therapy during pregnancy or the puerperium.

Physical Examination.—The infant was well nourished and did not appear critically ill. She was irritable, crying out at frequent intervals. The abnormalities were essentially limited to the extremities. The arms and legs were held immobile, and the patient screamed when they were touched (figure). The right wrist, though swollen and tender, was not reddened. It was held in volar flexion, with the thumb drawn across the palm, and the fingers were held in slight flexion, a position resembling that of "accoucheur's hand." The elbows, which were maintained in moderate flexion, were not swollen or tender. Definite swelling was present over the proximal phalanges of the left hand, most marked on the third finger. Questionable swelling of the phalanges of the right hand was also noted. There was no obvious swelling of the other joints, though the ankles were definitely tender. The legs were held in slight flexion at the hips and knees, and an attempt to extend them elicited a painful response. The heart sounds were normal.

Roentgen Examination.—A roentgenogram of the chest showed that the heart was of normal size and shape and the lungs were clear. Roentgenograms of all the extremities revealed no abnormality.

Electrocardiographic Examination.—The electrocardiogram (interpreted by Dr. Louis Katz) showed a pulse rate of 130 and a PR interval of 0.12 second. The QRS wave in lead I was inverted and in leads II and III it was elevated; the ST wave in lead I was also elevated. Sinus arrhythmia was present. The pulse rate and the other observations were considered to be within normal limits for the child's age. A second electrocardiogram made four days later was similar to the first.

Laboratory Data.—Infant: The blood count showed 4,090,000 erythrocytes and 21,800 leukocytes with 75 per cent polymorphonuclear neutrophils, 4 per cent polymorphonuclear eosinophils, 1 per cent polymorphonuclear basophils, 19 per cent lymphocytes, 1 per cent monocytes and 2 immature leukocytes. The microsedimentation rate was 18 mm. in one hour (normal, 10 mm.). Four days later it was 20 mm. in one hour, and two weeks after entry it had dropped to 11 mm. The ascorbic acid content of the blood was 0.768 mg. per hundred cubic centimeters. The blood calcium was 10.8 mg. per hundred cubic centimeters and the blood phosphorus 4.9 mg. Blood cultures on two occasions were sterile. Two cultures of material from the throat were negative for hemolytic streptococci. The reaction to a Mantoux test (1 : 1,000) was negative. Aspiration of material from the involved joints was considered, but because of the rapid clinical improvement, with subsidence of the joint symptoms, the procedure was deemed inadvisable.

Mother: Because of the rarity of the condition the baby was suspected of having, examinations of the mother were repeated, to exclude as far as possible any other conditions which might conceivably produce a similar picture. The reactions to the Wassermann and Kahn tests and the complement fixation test for gonorrhea were negative; the blood culture was sterile, and the culture of material from the throat revealed no hemolytic streptococci; cervical and vaginal smears were negative for gonococci, and an agglutination test for brucellosis also gave negative results.

Clinical Course.—On entry to the hospital the baby's rectal temperature was 103 F. She was given ½ grain (0.03 Gm.) of acetylsalicylic acid with ½ grain (0.03 Gm.) of sodium bicarbonate every four hours. Within four hours the temperature dropped to 98 F. She seemed more comfortable, and the following day there was definitely less tenderness in the joints and the swelling was less marked. The acetylsalicylic acid was stopped after twenty-four hours, after which the temperature remained normal for forty-eight hours; then it again rose to 101.6 F., the rise being accompanied by an exacerbation of the joint symptoms. Administration of the acetylsalicylic acid and sodium bicarbonate was resumed, and within twenty-four hours the temperature again dropped to normal. Acetylsalicylic acid was continued for six days, during which time the temperature remained normal and the joint symptoms disappeared. The baby behaved normally and took her feedings well. She was discharged from the hospital after two weeks, apparently entirely recovered.

For the past four years we have observed this child in the outpatient department. She was seen monthly until the age of 1 year and every three to six months thereafter. The reactions to Wassermann, Kahn and Mantoux tests when she was 3 months old were all negative. At no time has she had any symptoms which could be interpreted as being rheumatic. She has remained well except for several infections of the upper respiratory tract. There is no clinical evidence

of rheumatic heart disease. Repeated electrocardiograms and roentgenograms of the chest have been negative for cardiac involvement. She has recently shown signs of a primary tuberculous infection, with a positive reaction to the Mantoux test.

COMMENT

The diagnosis in this case pointed to rheumatic arthritis, despite the great rarity of that disease at this age. Considered, however, as possible diagnoses were congenital syphilis, gonorrheal arthritis and sepsis and, as less likely, tuberculosis, tetany and scurvy. Syphilis was ruled out by the negative maternal Wassermann reaction and by the normal roentgenograms of the infant's long bones. A subsequent Wassermann reaction of the infant's blood, at the age of 3 months, was also negative. Gonorrheal arthritis was excluded by the absence of a focus, such as conjunctivitis or vaginitis, and by the mother's normal vaginal smears and negative reaction to complement fixation tests for gonorrhea. Sepsis was ruled out by the blood cultures, which were sterile for both the mother and the baby, the absence of primary or metastatic foci in both the mother and the child and by the rapid recovery following the administration of salicylates. Scurvy in the newborn is extremely rare, if it occurs at all. The diagnosis was eliminated, however, by the normal level of ascorbic acid in the blood and by the absence of a history of vitamin C deficiency in the mother. Tuberculosis of the bones was not seriously considered and was ruled out by the normal roentgenograms, the time of onset, the negative reaction to the tuberculin test and the rapid subsidence of the symptoms. Tetany of the newborn was unlikely in view of the normal blood chemistry and the absence of neuromuscular hyperirritability.

The diagnosis of rheumatic fever rested on the definite occurrence of rheumatic fever in the mother, the presence in the infant of pain and swelling of the joints which responded to salicylates and the exclusion of other possible causes of swelling of the joints. We are aware that we are unable to offer substantiating pathologic evidence of rheumatic fever. It must also be pointed out that subsequent to the illness neither the mother nor the child showed signs of rheumatic carditis or other rheumatic manifestation. Despite these facts, we feel that we are justified in considering this case an example of probable rheumatic fever in a newborn infant.

From the standpoint of possible causes, the cases of rheumatic fever in the newborn fall into two fairly definite groups; in the first group are those instances in which the disease was manifest in the baby at birth or very shortly thereafter and in which the mother had rheumatic fever just before or at the time of delivery. In this group are the cases reported by Schaefer, Ferguson, Abrahams and Kissane and Koons.

The case of Kissane and Koons is undoubtedly the most convincing yet reported with regard to the possibility of placental transmission of the causative agent of rheumatic fever. The probable causes of the disease in this group of infants have been aptly stated by Swift.[12]

> The very rare occurrence of rheumatic fever in a newborn child of a mother suffering from active rheumatic fever suggests, on the one hand, the transmission in utero of a specific infectious agent, and, on the other hand, the transmission of some peculiar hereditary susceptibility; a third possibility is the transmission of a peculiar type of immunologically altered tissue from mother to offspring.

In the other group of cases, the disease developed in both the mother and the infant some time after delivery. In this group is the case of Guthrie and our case. It is of interest that in Guthrie's case the onset of the disease in the infant postdated that in the mother by one week, and in our case the infant became ill three days after onset in the mother. In these cases the placental transmission of the causative agent is less likely and instead the possibility of contagion, of direct contact or of transmission through the breast milk is suggested. If one agrees with Coburn that there is a latent period between the onset of the sensitizing infection and the occurrence of rheumatic fever, the possibility of placental transmission even in these cases must be admitted.

The incidence of cardiac involvement is worthy of note. In Ferguson's case autopsy showed the heart to be normal. In Abrahams' case 2 a murmur was present during life, but no examination was made after death, which occurred when the infant was 9 months old. In the case of Kissane and Koons there was irrefutable evidence of rheumatic heart disease at autopsy, and the history indicated that the heart had been involved at birth.

SUMMARY

A case of probable rheumatic fever in a breast-fed infant 10 days of age is reported.

12. Swift, H. F.: Rheumatic Fever, in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1931, vol. 1, p. 401.

Progress in Pediatrics

HYPERTENSION ASSOCIATED WITH UNILATERAL CHRONIC ATROPHIC PYELONEPHRITIS

OCCURRENCE IN A CHILD IN WHOM NO DECREASE OF BLOOD PRESSURE FOLLOWED NEPHRECTOMY

BEN BENJAMIN, M.D.
AND
MAX RATNER, M.D.
MONTREAL, CANADA

Hypertension is frequently associated with renal disease in children as well as in adults. Both kidneys may be involved, or one kidney may be the seat of disease. When the lesion was unilateral, at least so far as could be determined clinically, nephrectomy has been followed in some instances by a reduction in blood pressure for longer or shorter periods. In recent years increased interest in the study of experimentally produced hypertension has paved the way for enthusiastic clinical investigation, with a view to possible surgical therapy in apparently suitable, selected cases. It seems of importance to review the subject briefly, to emphasize the inadequacy of the present knowledge of the etiologic relation between hypertension and nephropathy and to record the case of a child in which, although it appeared reasonable to expect a favorable result, no decrease of blood pressure took place after nephrectomy.

Butler [1] described 6 cases of chronic pyelonephritis and arterial hypertension in children and pointed out that hypertension may be present before there is any appreciable diminution of renal function. Nephrectomy was performed in 2 cases, and the hypertension disappeared after the operation. The patient in 1 of these cases, a 10 year old girl was the subject of a more detailed report by Barney and Suby.[2] She was observed for twenty-one months after the removal of the kidney, and there was no recurrence of the elevation of blood pressure during

From the Departments of Pediatrics and Urology of the Jewish General Hospital.

1. Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889 (Nov.) 1937.

2. Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension, New England J. Med. **220**:744 (May 4) 1939.

that time. Patch, Rhea and Codnere [3] treated a 12 year old girl who had hypertension and unilateral chronic atrophic pyelonephritis by nephrectomy, after which the blood pressure fell to a normal level and had been maintained there up to the time of publication of their report (for six months). They reviewed 21 [4] cases from the literature in which unilateral nephropathy was associated with hypertension and improvement followed nephrectomy. In 3 cases congenital anomalies were present and in 8 hydronephrosis; in 10 there was pyelonephritis, described in 6 instances as atrophic. Only 4 [4] of the patients including their own, were children, and their ages ranged from 5½ to 12 years. The cases of 3 adult patients with chronic atrophic pyelonephritis and hypertension, which subsided after nephrectomy, were reported by Barker and Walters.[5] They also described the case of a 7 year old girl in which a similar favorable result was obtained. A more detailed account of this case was given by Kennedy, Barker and Walters.[6] The patient in this case had malignant hypertension and atrophic pyelonephritis of the left kidney, which was removed "as a measure of desperation," even though extensive retinitis was present. The blood pressure fell gradually, reaching the level of 110 mm. of mercury systolic and 85 mm. diastolic by the ninth postoperative day. Three months after operation it was normal, and the ocular fundi, which had begun to improve about the tenth postoperative day, showed no active retinal lesions.

REPORT OF A CASE

G. G., a 6 year old boy, was admitted to the ear, nose and throat service of the Jewish General Hospital on June 18, 1940 for tonsillectomy and adenoidectomy.

History.—He was an only child. The parents were well. The paternal grandmother had hypertension, which was first noted when she was about 45 years old. He was born at term after a normal pregnancy and labor. His birth weight was 6 pounds 5 ounces (2,864 Gm.). He thrived well during infancy. At 9 months of age he had pneumonia and left acute suppurative otitis media, from which he recovered uneventfully. He had frequent colds, but in the intervals between them he was considered by his parents to be well.

---

3. Patch, F. S.; Rhea, L. J., and Codnere, J. H.: Hypertension in a Girl of Twelve Associated with Unilateral Chronic Atrophic Pyelonephritis: Treated by Nephrectomy, Canad. M. A. J. **43**:419 (Nov.) 1940.

4. It appears that there were 22 cases reported on in the article and that 5 of the patients, including their own, were children; but this is erroneous, for according to a personal communication to us from Dr. Barney, 1 of the 2 cases of Butler [1] and that reported in detail by Barney and Suby [2] were the same.

5. Barker, N. W., and Walters, W.: Hypertension and Chronic Atrophic Pyelonephritis, J. A. M. A. **115**:912 (Sept. 14) 1940.

6. Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, Am. J. Dis. Child. **61**:128 (Jan.) 1941.

Tonsillectomy and Adenoidectomy.—On admission, physical examination and urinalysis gave normal results. About three hours after tonsillectomy and adenoidectomy were performed, hemorrhage from the left tonsillar fossa occurred. It was controlled by a pack in the fossa, over which the anterior and the posterior pillars were sutured together. The pack was removed the following day, and the throat healed normally thereafter. His blood pressure, measured for the first time, was 190 mm. of mercury systolic and 110 mm. diastolic.

Investigation Regarding Hypertension.—He was transferred to the pediatric service for investigation regarding the hypertension. The only abnormal physical sign at this time was pallor, due to secondary anemia. He weighed 42 pounds 12 ounces (19.4 Kg.). His height was 45½ inches (116 cm.). The red cell count was 3,100,000 per cubic millimeter of blood, the white cell count was 24,000 and the hemoglobin content (determined with the Evelyn photoelectric colorimeter) was 54 per cent (8.42 Gm. per hundred cubic centimeters). The differential count showed 55 per cent polymorphonuclears (24 per cent immature and 31 per cent segmented), 24 per cent lymphocytes, 3 per cent myelocytes, 8 per cent metamyelocytes and 10 per cent monocytes. The thrombocyte count was 240,000 per cubic millimeter. The thrombocytes were normal in size and shape. The bleeding time (Duke) was one and one-half minutes. Blood coagulation (formation of fibrin in a drop of venous blood) started in four and a half minutes and was completed in ten minutes. Clot retraction time was normal.

He was given three transfusions of citrated blood, totaling 500 cc.; iron was administered orally, and he was fed a full diet. On July 20 the red cell count was 4,800,000 per cubic millimeter, the white cell count was 8,700 and the hemoglobin content was 74 per cent (11.54 Gm. per hundred cubic centimeters). The temperature was normal. The pulse rate varied between 90 and 100 and the respiratory rate between 20 and 30 per minute. The Wassermann and Kline tests of the blood gave negative reactions. Repeated urinalyses showed clear, light amber urine with a specific gravity ranging from 1.011 to 1.022, no albumin and no sugar; no pus, blood or casts could be demonstrated microscopically. Urine concentration tests gave normal results on two occasions; they showed ranges of specific gravity from 1.001 to 1.015 and 1.006 to 1.017, respectively. The urea clearance was 67 per cent of normal. In a phenolsulfonphthalein test 85 per cent of the dye was excreted in the first hour and 5 per cent in the second; a second test showed that 75 per cent was excreted in the first hour and 20 per cent in the second. Examination of the blood showed sugar, 115 mg. per hundred cubic centimeters; nonprotein nitrogen, 23 mg.; urea, 26 mg.; creatinine, 0.65 mg.; uric acid, 2.94 mg., and chlorides, 562.8 mg. The optic fundi were normal. An electrocardiogram was normal. Roentgenologic examinations showed that there was no abnormality of the cardiac shadow, the lungs were clear, the long bones were normal and there was no evidence of calculus in the urinary tract. Cystoscopic examination revealed that the bladder and the ureteral orifices were normal. Both ureters were catheterized; 1.5 cc. of urine obtained from the right showed good urea concentration, but no urea was demonstrated in 1.0 cc. from the left. An excretory urogram showed that the right renal pelvis and ureter were normal, with a good concentration of the dye, but the left renal pelvis and ureter were not visualized in any of the urograms taken at intervals of fifteen minutes up to one hour after the injection of 12 cc. of diodrast, which indicated impaired function of the left kidney.

Nephrectomy.—The left kidney was removed on July 23.

Blood Pressure Readings.—The range of the blood pressure prior to operation was from 190 mm. of mercury systolic and 110 mm. diastolic to 145 mm. systolic and 100 mm. diastolic; during the operation the range was from 240 mm. systolic and 120 mm. diastolic to 142 mm. systolic and 100 diastolic, and postoperatively and during convalescence it ranged from 230 mm. systolic and 126 mm. diastolic to 150 mm. systolic and 90 mm. diastolic. On August 8, the day the boy left the hospital, the blood pressure was 172 mm. systolic and 128 mm. diastolic. He has now been under observation for six months [7] since the left kidney was removed, and the hypertension has continued unabated throughout this period. Just before he was discharged from the hospital the concentration of the urine, the urea clearance and the results of phenolsulfonphthalein tests were normal.

Fig. 1.—Retrograde bilateral pyelogram, showing the relatively normal right renal pelvis and ureter and the markedly distorted left renal pelvis with absence of calices.

Pathologic Report (Dr. M. A. Simon).—The specimen consisted of the left kidney and a portion of the attached ureter, having a total weight of 4 Gm. The kidney measured 22 by 13 by 7 mm. (fig. 2). It was somewhat lobulated and firm. The capsule was slightly thickened and intimately adherent, particularly over the midportion, where a number of fibroadipose tags were adherent to it. The outer surface of the kidney was smooth, gray and mottled red. It cut with increased resistance. The cut surface (fig. 3) revealed only a few fragments of recognizable renal parenchyma, with sharp demarcation between the cortex and the medulla. The central portion was completely replaced by tough, yellowish gray tissue, which surrounded the pelvis and almost completely replaced the renal

7. Dr. D. Barza made the measurements of the blood pressure during this time.

parenchyma. The pelvis was small, the calices were obliterated, the wall was thickened, the mucous membrane was wrinkled and focal submucosal hemorrhages were seen throughout. The portion of ureter attached to the kidney measured 2.5 cm. in length. Its lumen was patent, the wall was thickened and the mucous membrane showed focal hemorrhages.

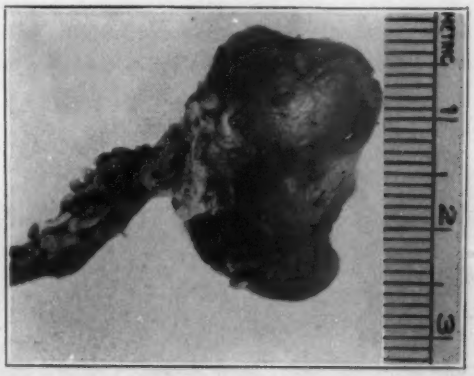


Fig. 2.—Photograph of the left kidney. Note the marked reduction in size, the irregular thickening of the fibrous capsule and the roughly lobulated appearance.

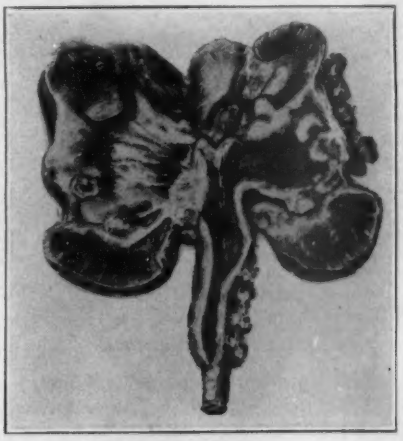


Fig. 3.—Photograph of a drawing (actual size) of the longitudinally cut surface of the left kidney. Note the extensive fibrous replacement of the midportion of the kidney, with retention of only slightly involved renal parenchyma at both poles, and the marked thickening of the pelvis and the ureter, with hemorrhage into the former.

Microscopic Examination: Complete longitudinal sections through the kidney showed replacement of one half of the kidney in its midportion by fibrous connective tissue, in which a number of slightly dilated urinary tubules were present. These tubules were lined by single and multiple layers of low cuboidal epithelium

and appeared to have no connection with the glomeruli. In the fibrous connective tissue there was a sparse infiltration with lymphocytes, occasional plasma cells and rare polymorphonuclear leukocytes. In this fibrous portion (fig. 4) thick-walled blood vessels were encountered, the thickening occurring primarily in the media. At either pole the changes varied from irregular fibrosis within the renal parenchyma to areas in which no significant pathologic changes could be seen. Immediately adjacent to the fibrous area in the midportion there was irregular, diffuse fibrosis throughout the renal parenchyma, which was infiltrated with lymphocytes and rare polymorphonuclear leukocytes. Many of the tubules were

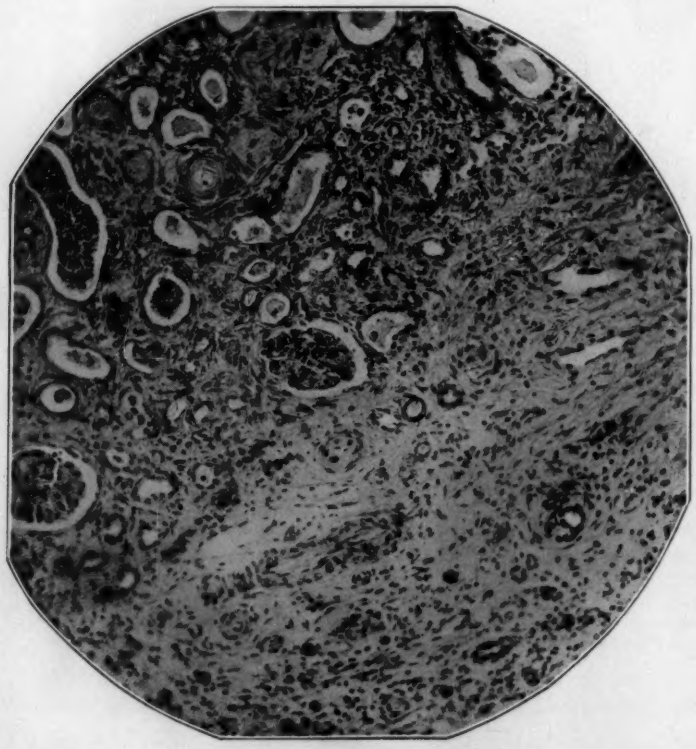


Fig. 4.—Photomicrograph of a section of the left kidney through a region of fibrosis with adjacent parenchyma. Note the fibrosis of the parenchyma, with lymphocytic infiltration, thickening of the arterioles and slight shrinkage of the glomeruli, and the presence of hyaline and leukocyte casts in the tubules. Medium power.

dilated and contained red, homogeneous casts. Occasionally these casts had a blue tinge, and in some instances polymorphonuclear leukocytes could be observed within the tubules. The glomerular changes varied from complete fibrosis to slight, irregular fibrosis of individual lobules of the glomerular tufts. The arterioles showed only a minimal degree of medial thickening, and the caliber of their lumens was only questionably reduced. In the relatively uninvolved portions at either pole the tubular epithelium showed minimal degrees of cloudy swelling, and accumulations of pink-staining, homogeneous material were seen in the subcapsular

spaces. No distortion of the architecture was seen in the portions of the kidney in which the parenchyma remained relatively uninvolved. The capsule was irregularly thickened and intimately adherent, particularly over the area of scarring, and was infiltrated with lymphocytes.

The entire picture might be the result of an inflammatory lesion. No evidence of hypoplasia was seen, although the possibility that this kidney was smaller originally than the one on the opposite side cannot be excluded. If the inflammatory changes occurred at an early age, the reduction in size of this kidney could be explained entirely on the basis of contracture following inflammation.

Diagnosis.—The diagnosis was chronic atrophic pyelonephritis and chronic ureteritis.

COMMENT

Hypertension is not a disease entity. It may accompany abnormalities in which there is no disturbance of the function of the kidney, for example, dysfunction of the endocrine glands. Many patients with chronic hypertension are said to have so-called essential hypertension. Fishberg [8] included under this concept "those cases which neither clinically nor anatomically can be demonstrated to have evolved from antecedent inflammatory disease of the kidneys or urinary obstruction." There is both experimental and clinical evidence that in certain instances hypertension is due to disturbances in the function of the kidney. Hypertension which arises in association with disturbances of the kidneys is commonly termed renal hypertension.

Since hypertension sometimes disappears after the removal of a diseased kidney, it might be inferred that a cause and effect relation existed between the diseased organ and the symptom. Apparently the explanation is much more complicated. This is suggested by the fact that the elevation of blood pressure has recurred in many of the cases in which the patient was observed for a sufficient time after nephrectomy, although the possibility of the existence of pathologic changes in the remaining kidney which could not be detected clinically must be conceded.

The pathogenesis of clinical hypertension has not as yet been clearly established. Whether the same mechanism is basically responsible for renal and for so-called essential hypertension has not been answered conclusively. Pearman, Thompson and Allen [9] suggested that the two conditions are not necessarily identical, even though, like Schroeder and Steele [10] and others, they found urographic evidence of renal lesions in an appreciable proportion of their cases of essential hypertension.

8. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 555.

9. Pearman, R. O.; Thompson, G. J., and Allen, E. V.: Urographic Evidence of Renal Lesions in a Series of Patients Suffering from Essential Hypertension, Proc. Staff Meet., Mayo Clin. **15**:467 (July 24) 1940.

10. Schroeder, H. A., and Steele, J. M.: Abnormalities of the Urinary Tract in "Essential Hypertension," Proc. Soc. Exper. Biol. & Med. **39**:107 (Oct.) 1938.

There is no absolutely characteristic picture which can be demonstrated post mortem in the kidneys or elsewhere in all cases of hypertension. On the basis of pathologic studies Kimmelstiel and Wilson [11] could not decide in the majority of instances whether they were dealing with primary "vascular" or secondary "renal" hypertension. They came to the conclusion [12] that the glomerular lesions in cases of pyelonephritis were indistinguishable from the focal glomerulitis which is found in cases of essential hypertension. In comparing the histologic observations in cases in which there was and was not hypertension, Moritz and Oldt [13] stated that the most common abnormality in cases of chronic hypertension was arteriolar sclerosis and that so far as its association with hypertension was concerned the only significant site was the kidney. Weiss and Parker,[14] in a study of cases of pyelonephritis, showed that bilateral marked hyperplastic arteriolar sclerosis was usually associated with severe hypertension but that in some of the cases in which the arteriolar sclerosis was unilateral there was hypertension and in others there was not. Blackman [15] demonstrated arteriosclerotic narrowing of the lumens of the main renal arteries in a considerably greater proportion of a group of 50 cases of chronic hypertension than in a comparable group in which the blood pressure was not abnormally high. Braasch, Walters and Hammer [16] observed that the incidence of hypertension was low in cases in which nephrectomy was performed for pyelonephritis without atrophy and sclerosis. These changes were present in the excised kidneys of most of the hypertensive patients. Occasionally, however, marked vascular sclerosis was seen in the kidney of a patient whose blood pressure was not elevated. They stated that hypertension would be relieved by operation in approximately 70 per cent of the cases in which it accompanies atrophic pyelonephritis. Reviewing the cases of 150 patients who had been subjected to nephrectomy, Crabtree and Chaset [17] found that hypertension was not frequent,

---

11. Kimmelstiel, P., and Wilson, C.: Inflammatory Lesions in the Glomeruli in Pyelonephritis in Relation to Hypertension and Renal Insufficiency, Am. J. Path. **12**:99 (Jan.) 1936.

12. Kimmelstiel, P., and Wilson, C.: Benign and Malignant Hypertension and Nephrosclerosis, Am. J. Path. **12**:45 (Jan.) 1936.

13. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679 (Sept.) 1937.

14. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221 (Sept.) 1939.

15. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **45**:353 (Nov.) 1939.

16. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, J. A. M. A. **115**:1837 (Nov. 30) 1940.

17. Crabtree, E. G., and Chaset, N.: Vascular Nephritis and Hypertension, J. A. M. A. **115**:1842 (Nov. 30) 1940.

although vascular changes were present in a high percentage of the cases. Operation was not followed by any appreciable reduction of the blood pressure. They came to the conclusion that the pathologic and anatomic changes in cases of renal hypertension are less important than an as yet unknown physiologic factor. In our case the main pathologic features consisted of extensive fibrosis, marked diminution of the normal renal tissue and thickening of the arterioles in the fibrotic regions, a picture similar to that described in cases of unilateral chronic pyelonephritis associated with elevated blood pressure which decreased after nephrectomy.

The blood pressure of animals has been raised experimentally by procedures affecting the kidneys in a number of ways. These have consisted chiefly of partial obstruction of the ureters,[18] partial occlusion of the renal vein,[19] ligation of branches of the renal arteries,[20] resection of large portions of both kidneys,[21] irradiation,[22] enveloping the kidney with cellophane or silk [23] and partial occlusion of the renal arteries.[24] Goldblatt and his colleagues [25] produced permanent hypertension in dogs

18. Rautenberg, E.: Erzeugung chronischer Nierenerkrankungen mit folgender Blutdrucksteigerung und Arteriosklerose, Deutsche med. Wchnschr. **36**:551, 1910. Harrison, T. R.; Mason, M. F.; Resnick, H., and Rainey, J.: Changes in Blood Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**:280, 1936.

19. Pedersen, A. H.: A Method of Producing Experimental Chronic Hypertension in the Rabbit, Arch. Path. **3**:912 (May) 1927.

20. Pässler and Heineke: Versuche zur Pathologie des Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch. **9**:99, 1905. Janeway, T. C.: Note on the Blood Pressure Changes Following Reduction of the Renal Arterial Circulation, Proc. Soc. Exper. Biol. & Med. **6**:109, 1908. Hartwich, A.: Der Blutdruck bei experimenteller Urämie und partieller Nierenausscheidung, Ztschr. f. d. ges. exper. Med. **69**:462, 1930.

21. Cash, J. R.: A Preliminary Study of the Blood Pressure Following Reduction of Renal Substance with a Note on Simultaneous Changes in the Blood Chemistry and Blood Volume, Bull. Johns Hopkins Hosp. **35**:168 (June) 1924.

22. Hartman, F. W.; Bolliger, A., and Doub, H. P.: Experimental Nephritis Produced by Irradiation, Am. J. M. Sc. **172**:487 (Oct.) 1926.

23. Page, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis, J. A. M. A. **113**:2046 (Dec. 2) 1939.

24. Goldblatt, H.; Lynch, J.; Hanzal, R, F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**:347 (March) 1934.

25. (*a*) Goldblatt, H.: Studies on Experimental Hypertension: The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69 (July) 1937; (*b*) Experimental Hypertension Induced by Renal Ischemia, Bull. New York Acad. Med. **14**:523 (Sept.) 1938. (*c*) Goldblatt, Lynch, Hanzal and Summerville.[24]

and monkeys by constricting both renal arteries with clamps. When only one kidney was thus rendered ischemic the resulting hypertension was transient. Removal of the clamp or of the ischemic kidney resulted in a return of the blood pressure to a normal level. Wilson and Byrom [26] succeeded in producing sustained hypertension in rats by partial occlusion of one renal artery. They found histologic changes in the opposite kidney which appeared to be identical with the lesions of malignant hypertension in man. They came to the conclusion that these changes were due to the vascular strain imposed by rapidly developing hypertension and that renal failure apparently played no part in their origin. Their results lent weight to the conception that malignant hypertension is a form of essential hypertension in which the renal lesions are a secondary manifestation. Wood and Cash [27] were able to maintain an elevation of blood pressure in a dog for two years by constriction of the right renal artery with a clamp. They expressed the belief that the hypertension which followed subtotal nephrectomy, ligation of the renal arteries and renal ischemia resulted from the same fundamental cause, although no explanation of the exact mechanism was offered. It is interesting that hypertension has been produced in animals by other methods which do not affect the kidneys directly.[28] Nowak and Walker [28b] obtained a sustained elevation of blood pressure in a dog after ligation of the cerebral arteries.

The true nature of experimental hypertension due to renal ischemia has not yet been disclosed. It does not appear to rest on a neurogenic basis. Goldblatt, Gross and Hanzal [29] by bilateral splanchnicotomy, Freeman and Page [30] by sympathectomy and Page [31] by denervation of both kidneys were unable to alter the course of this type of hyper-

---

26. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension: Experimental Evidence, Lancet **1**:136 (Jan. 21) 1939.

27. Wood, J. E., Jr., and Cash, J. R.: Experimental Hypertension: Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, J. Clin. Investigation **15**:543 (Sept.) 1936.

28. (*a*) Dixon, W. E., and Heller, H: Experimentelle Hypertonie durch Erhöhung des intracraniellen Druckes, Arch. f. exper. Path. u. Pharmakol. **166**:265, 1932. (*b*) Nowak, S. J. G., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension, New England J. Med. **220**:269 (Feb. 16) 1939.

29. Goldblatt, H.; Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension: Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, J. Exper. Med. **65**:233 (Feb.) 1937.

30. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of Renal Artery in Sympathectomized Dogs, Am. Heart J. **14**:405 (Oct.) 1937.

31. Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, Am. J. Physiol. **112**:166 (May) 1935.

tension. In this connection it is noteworthy that splanchnicectomy [32] has been followed by a decline in blood pressure in some cases of hypertension. Houssay and Fasciolo [33] transplanted the ischemic kidney of a living dog in which hypertension was produced to a second dog and anastomosed the constricted renal artery of the former to the carotid artery of the latter and the renal vein of the former to the jugular vein of the latter. Hypertension occurred in the latter dog. This tends to support the hypothesis of the elaboration of a substance by the ischemic kidney which is in some manner responsible for a pressor effect. Fasciolo, Houssay and Taquini [34] demonstrated that the substance responsible for the raising of the blood pressure was active in the absence of the adrenals and that healthy renal tissue was capable of diminishing its effect. Conflicting results have been obtained with the use of injections of extracts of ischemic kidneys: Harrison, Blalock and Mason [35] and Prinzmetal and Friedman [36] obtained rises in blood pressure, while Page [37] did not. Glenn and Lasher [38] showed that thyroidectomy neither prevented nor abolished hypertension due to renal ischemia. Goldblatt [25a] and Blalock and Levy [39] abolished the effect of renal ischemia on blood pressure by the removal of both adrenal glands, and Page and Sweet [40] obtained similar results by extirpation of the pituitary gland.

---

32. Adson, A. W.; Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, Surg., Gynec. & Obst. **62**:314 (Feb., no. 2 A) 1936. Freyberg, R. H., and Peet, M. M.: Effect on Kidney of Bilateral Splanchnicectomy in Patients with Hypertension, J. Clin. Investigation **16**:49 (Jan.) 1937. Smithwick, R. H.: Technique for Splanchnic Resection for Hypertension: Preliminary Report, Surgery **7**:1 (Jan.) 1940.

33. Houssay, B. A., and Fasciolo, J. C.: Experimental Hypertension, J. A. M. A. **109**:2002 (Dec. 11) 1937.

34. Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood Pressure Raising Secretion of the Ischemic Kidney, J. Physiol. **94**:281 (Dec. 14) 1938.

35. Harrison, T. R.; Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:38 (Oct.) 1936.

36. Prinzmetal, M., and Friedman, B.: Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:122 (Oct.) 1936.

37. Page, I. H.: Vaso-Pressor Action of Extracts of Plasma of Normal Dogs and Dogs with Experimentally Produced Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:112 (Oct.) 1936.

38. Glenn, F., and Lasher, E. P.: Effect of Total Thyroidectomy upon Production and Maintenance of Experimental Hypertension, Proc. Soc. Exper. Biol. & Med. **38**:158 (Feb.) 1938.

39. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826 (Nov.) 1937.

40. Page, I. H., and Sweet, J. E.: Extirpation of Pituitary Gland on Arterial Blood Pressure of Dogs with Experimental Hypertension, Proc. Soc. Exper. Biol. & Med. **34**:260 (March) 1936.

This work suggests a possible endocrine factor in the production of hypertension by renal ischemia.

It is not hard to envisage the counterpart of experimental renal ischemia in a patient as a result of narrowing of the renal artery or arterioles of a kidney, but it may be difficult to be certain that such a condition is present in a specific instance and that there is no abnormality of the other kidney or elsewhere in the body which might be of etiologic significance in relation to the hypertension. In a number of the cases recorded in which hypertension was reduced after nephrectomy gross abnormalities which restricted the flow of blood through the renal artery were discovered. Such lesions have been described as a plug of smooth muscle partially occluding the renal artery of an ectopic kidney in a boy 5½ years old,[41] a Wilms tumor constricting the renal artery in a 7 year old girl [42] and a Wilms tumor,[43] lymphosarcoma [44] and atheromatous plaques [45] which produced a similar effect in adults. Schroeder and Fish [46] gave criteria for the selection of patients suitable for operation, but they expressed the opinion that the information at present available is unsatisfactory for the estimation of the value of nephrectomy in cases of unilateral nephropathy and hypertension.

The facts that only one kidney is involved so far as can be demonstrated clinically, that there is marked loss of function of the diseased kidney, that renal function is not demonstrably impaired and that there is no retinal or any other clinically detectable abnormality supply no guarantee that nephrectomy will surely be followed by a reduction of blood pressure.

Hypertension is not present in all cases of pyelonephritis. In some instances it may be present early, while in others it may not appear until late in the course of the disease. It may develop without any appre-

---

41. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611 (May) 1938.

42. Koons, K. M., and Ruch, M. K.: Hypertension in a Seven-Year-Old Girl with Wilms' Tumor Relieved by Nephrectomy, J. A. M. A. **115**:1097 (Sept. 28) 1940.

43. Bradley, J. E., and Pincoffs, M. C.: Association of Adenomyosarcoma of Kidney (Wilms' Tumor) with Arterial Hypertension, Ann. Int. Med. **11**:1613 (March) 1938.

44. Blatt, E., and Page, I. H.: Hypertension and Constriction of Renal Arteries in Man: Report of a Case, Ann. Int. Med. **12**:1690 (April) 1939.

45. Freeman, G., and Hartley, G.: Hypertrophy in a Patient with a Solitary Ischemic Kidney, J. A. M. A. **111**:1159 (Sept. 24) 1938. Leiter, L.: Unusual Hypertensive Renal Disease, ibid. **111**:507 (Aug. 6) 1938.

46. Schroeder, H. A., and Fish, G. W.: Studies on "Essential Hypertension": Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. M. Sc. **199**:601 (May) 1940.

ciable impairment of renal function, or the latter may be impaired with little or no elevation of the blood pressure. The explanation for the presence or absence of hypertension in such cases is not clear.

SUMMARY

A 6 year old boy who had hypertension associated with pronounced atrophic pyelonephritis, and marked functional impairment of one kidney and no evidence of any other abnormality was subjected to nephrectomy. There was no decline of the systolic or the diastolic blood pressure immediately after the operation or during the following six months.

The relation between hypertension and renal disease requires further elucidation. It appears impossible at present to formulate definite criteria for the selection of cases of unilateral nephropathy and hypertension in which it may be expected that nephrectomy will be followed by a reduction of blood pressure in every instance. For any child who has chronic hypertension associated with renal disease a urologic examination is advisable. If the examination clearly demonstrates the presence of a unilateral renal lesion and there is no contraindication to operation, nephrectomy may be justified. The hypertension may disappear after the operation, but the possibility that such a favorable result may not be obtained should be borne in mind.

News and Comment

GENERAL NEWS

Directory of Medical Specialists.—A second edition of the *Directory of Medical Specialists* has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February 1942, with its contents complete to January 1. The directory is the official publication of the Advisory Board and will list the names of approximately 18,000 diplomates of the fifteen American boards examining candidates for certification in the specialties. This is an increase of 4,000 over the first edition, which was issued early in 1940. There will be a geographic listing of the diplomates, with completely revised biographic data for each; there will also be an alphabetic index, with addresses and specialty designations, and the plan of organization, officers and requirements for admission to the examinations of each American board will be fully outlined.

Information not found in the first edition will be included in the second, such as details about formal training and military appointments.

The names of all specialists who have been formally certified by one of the American boards will be included.

The publication is issued through the Columbia University Press, New York. The secretary of each specialty board serves on the advisory editorial board, and Dr. Paul Titus, 1015 Highland Building, Pittsburgh, secretary-treasurer of the American Board of Obstetrics and Gynecology, is the directing editor.

Pamphlet on Nursing Care of Patients with Poliomyelitis.—The National Foundation for Infantile Paralysis announces the publication of a Spanish translation of the pamphlet "The Nursing Care of Patients with Infantile Paralysis," by Jessie L. Stevenson, R.N. This pamphlet, illustrated by line drawings, was prepared by the National Organization for Public Health Nursing, to which the author is a consultant in orthopedic nursing, as a part of a project in orthopedic nursing sponsored by the Foundation. It is intended to assist the public health nurse and others responsible for the home care of patients with infantile paralysis during and following epidemics of the disease. Copies either in Spanish or in English are available, free on request, from the National Foundation for Infantile Paralysis, 120 Broadway, New York.

Courses in Child Development and Parent Education.—The University of Iowa will give its usual summer courses in child development and parent education from June 9 to August 1 this year.

PERSONAL NEWS

Appointment Announced.—Dr. Richard M. Smith has been appointed vice chairman of Section 3 (Public Health and Medical Aspects of Nutrition with Special Reference to the Needs of Women and Children) of the National Conference on Nutrition in Defense.

DEATHS

Dr. G. W. Kutscher Jr., of Asheville, N. C., a well known pediatrician, died recently.

Dr. Robert G. Sharp, of San Diego, Calif., who has for many years practiced pediatrics in that city, died recently.

Dr. Paul H. Herron, a pediatrician of Oak Ridge, La., died recently from electric shock while taking a roentgenogram.

Obituaries

HENRY LARNED KEITH SHAW, M.D.

1873-1941

Dr. Henry Larned Keith Shaw died at his home in Guilderland, near Albany, N. Y., March 27, 1941, in his sixty-eighth year. Pediatrics has lost another of its pioneers, for he had been actively engaged in practice, in Albany, for almost forty years.

Born at Chaumont, Jefferson County, N. Y., on Aug. 8, 1873, he attended school in Cheshire, England, for five years, his father being in the consular service. Returning to this country at the age of 12, he attended Trinity School, Tivoli-on-Hudson, N. Y., and the Pennsylvania Military Academy and entered Cornell University in the fall of 1891. In his freshman year he was captain of his class crew, which established a world record on Lake Minnetonka. He also rowed on Cornell's victorious varsity crew the following year.

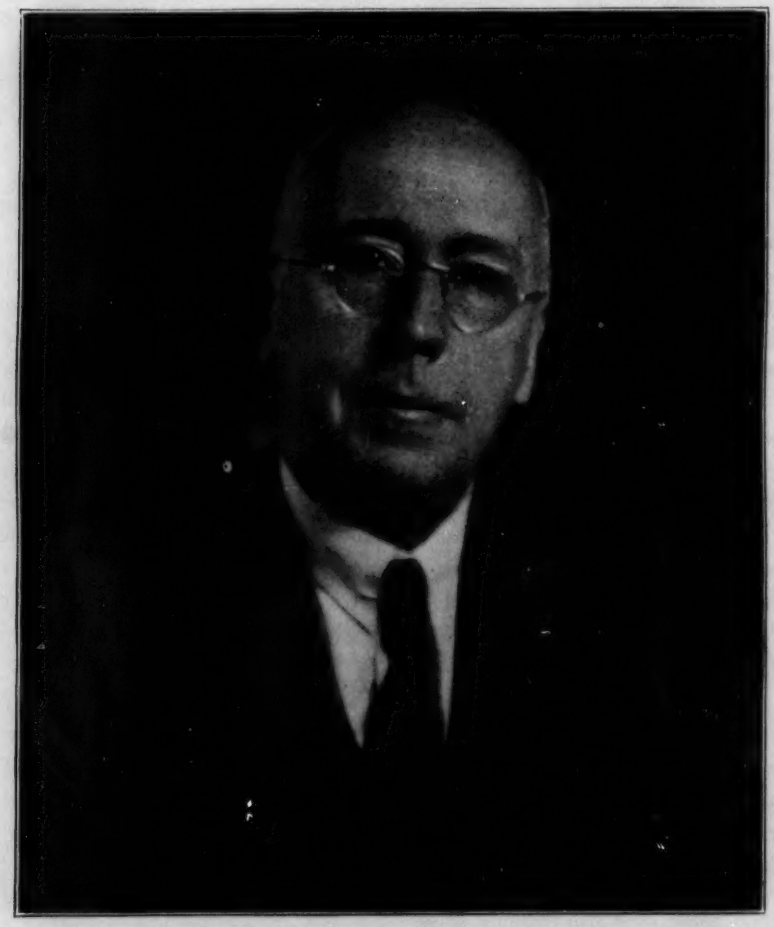
In the fall of 1893 he entered Albany Medical College, from which he received the degree of Doctor of Medicine in 1896. He interned at St. Peter's Hospital, Albany, and at Utica State Hospital. He then spent two years abroad, serving as resident at the Munich Frauenklinic, under Escherich at the Annaspital in Vienna, under Spitzey at the Children's Hospital in Graz and at the Children's Hospital in Manchester, England.

He returned to America in 1900 and immediately started practice in Albany. With his splendid training, his alert mind, his charming personality and his endless energy, it is not strange that he immediately won wide recognition throughout a large area. Two years after starting practice, at the advanced age of almost 29 years, he was elected to the American Pediatric Society. In 1929 he was its president.

Dr. Shaw was much interested in pediatric education and in 1905 became instructor in pediatrics at the Albany Medical College, where he served continually in various grades up to professor of pediatrics. He was long connected with the Albany Hospital and was chief of its pediatric service at the time of his death.

St. Margaret's House and Hospital, in Albany, was close to his heart. He was connected with it almost from the time he began to practice. He helped to establish its most successful school for training nurses for well babies and was pediatrician in chief for many years. He took a great personal, as well as professional, interest in it.

Keenly interested in preventive pediatrics, Dr. Shaw was long connected with the American Association for the Study and Prevention of Infant Mortality. He was president of this organization in 1921, when it was functioning under its second name, the American Child Hygiene Association. Believing strongly in the importance of lay edu-



HENRY LARNED KEITH SHAW, M.D.
1873-1941

cation in child health, he wrote for the *Delineator, Parents' Magazine* and *New York Tribune,* contributing articles noteworthy for their clarity, their accuracy and their practical common sense.

In 1912, the late Dr. Porter, then Commissioner of Health of New York State, called on him for advice on conducting child health work and appointed him consulting pediatrician to the New York State

Department of Health. When New York established the first state division of child hygiene in the country two years later, he became its director; later he acted as consultant. He was the valued advisor of five commissioners of health.

Thoroughly convinced of the importance of clean milk, in 1912 he established at his farm in Guilderland a dairy, which supplied Albany with its first certified milk. The dairy continued to operate until after the first World War.

Dr. Shaw was prominent in the medical societies of his locality. He organized, and was chairman of, the first pediatric section of the Medical Society of the State of New York. He was at one time president of the Albany County Medical Society. An indefatigable reader himself, he founded and took an active interest in a medical journal club, composed of the younger pediatricians in Albany and its neighborhood. He was its most regular attendant.

Dr. Shaw entered the United States Army in the first World War. His ambition was to be sent abroad, but it was his fate to be so valuable as intelligence officer in charge of counterespionage at Oglethorpe, Ga., that he never succeeded, though his orders to go came just before the armistice put an end to his hope.

At the time of his death, Dr. Shaw was chief pediatrician of the Albany Hospital, chief of staff of St. Margaret's House and Hospital and consultant to the Anthony N. Brady Maternity Home, the Memorial Hospital of Greene County, Catskill, N. Y., Vassar Brothers Hospital, Poughkeepsie, N. Y., Little Falls Hospital, Glens Falls Hospital and the Mary McClellan Hospital, Cambridge, N. Y.

Simple in his way of life, tireless in his activity, honest to the last degree with himself and with others, he was a splendid citizen and physician and a loyal and devoted friend. Life without active work would have been utter tedium to him. That his death came almost without warning is as he would have chosen.

FRED MOORE, M.D.

1883–1941

Dr. Fred Moore died on April 8 at his home in Des Moines, Iowa, of maligant disease of the stomach and liver. He was 58 years old. Surviving him are his widow and 3 children, Fred Brown, Elizabeth Pauline and Richard Morris. Dr. Moore was born at Harlan, Iowa, on May 10, 1883. He received the degree of Bachelor of Science from the University of Iowa in June 1906 and the degree of Master of Science from the University of California in June 1907.

His medical education began at Western Reserve University School of Medicine, Cleveland, where he was a member of the freshman class in 1907. He completed his undergraduate medical education, however, at the University of Iowa and received the degree of Doctor of Medicine from that institution in June 1911. The following year he completed a general internship at Montreal General Hospital. He engaged in private practice in his home state for a brief period but then entered Johns Hopkins Hospital in the pediatric service of Dr. John Howland. He came to Des Moines late in the summer of 1915 and began the practice of pediatrics.

In 1917 he was appointed director of the school health service of Des Moines, a position which he held to the time of his death. His work in this connection was outstanding and gained nationwide attention. Recently, in collaboration with Dr. John W. Studebaker, United States Commissioner of Education, he prepared a small book on the Des Moines plan for school health work, which is having a national circulation.

Dr. Moore was a member of the Central State Pediatric Society for many years, and when the American Academy of Pediatrics was organized in 1931 he was enrolled among the founder members. He was also a diplomate and a member of the group of founders of the American Board of Pediatrics. He served on the School Health Committee at the first White House Conference on Child Health and Protection, called by President Hoover in 1930. He was elected to the House of Delegates of the American Medical Association in 1931 and had served continuously in that capacity ever since. In 1934 his nomination as a member of the Council on Medical Education and Hospitals for the term of seven years was approved by the House of Delegates.

He was active in this work up to the time of his death and had attended a meeting of the Council in Washington, D. C., in November of last year.

Dr. Moore was one of the outstanding pediatricians of America. His loss will be keenly felt in the many spheres of activity in which he was engaged. He was an indefatigable worker and was held in the utmost respect by his host of friends and colleagues.

Abstracts from Current Literature

Anatomy and Physiology

THE HYPOGLOSSAL NERVE IN HUMAN EMBRYOS. ANTHONY A. PEARSON. J. Comp. Neurol. **71**:21 (Aug.) 1939.

Pearson presents the second in a series of studies on the development and analysis of the cranial nerve components in human embryos. Six human embryos, between 17 and 46 mm. in crown-rump length, were available. In the 25 mm. embryo the hypoglossal nucleus showed as a prolongation of the cervical ventral gray column into the medulla. At the 45 mm. stage the cell column of the hypoglossal nerve showed division into a dorsal and a ventral cell column. The cephalic end of the dorsal column was divided into a medial and a lateral part. The twelfth nerve was found to have communicating branches which connected it with the first and second cervical nerves, the superior cervical sympathetic ganglion or the sympathetic trunk, the carotid plexus, the lingual nerve and sometimes with the hypoglossal nerve of the other side. Pearson found no evidence that either Roller's nucleus or the nucleus intercalatus contributed to the hypoglossal nerve.

FRASER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Biochemistry; Bacteriology, and Pathology

STUDIES ON A PURIFIED ANTIGEN FROM BRUCELLA. P. MORALES-OTERO and L. M. GONZALEZ, Am. J. M. Sc. **199**:810 (June) 1940.

The authors describe a method for the preparation, from Brucella cells, of a purified protein derivative of a fairly constant chemical composition, that can be measured accurately and constitutes a good antigen.

The preparation has been used successfully as an antigen in complement fixation tests and in determining cutaneous hypersensitiveness to Brucella in man and in laboratory animals.

The incidence of positive reactors to the skin test in Puerto Rico, where Brucella abortus infection is prevalent in cattle, was 24.7 per cent in contact groups and 4.2 per cent in groups from the general population consuming raw milk from infected sources. The authors were unable to find any reactors in the group examined on the island of St. Thomas, where infection is not known to exist.

EMKE, Omaha.

BACTERIOSTATIC ACTION OF SULFANILAMIDE. A. FLEMING, J. Path. & Bact. **50**:69, 1940.

Experiments are described showing the bacteriostatic power of sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine; preparation used, M & B 693) in broth, serum and blood, with or without leukocytes, and on solid culture medium. All such experiments show that these substances have a powerful bacteriostatic action on small numbers of Streptococcus pyogenes but that the action on massive implants is negligible. Sulfanilamide injected intravenously into a rabbit immediately confers on the blood increased bacteriostatic power. The significance of this is discussed. Thick suspensions of bacteria in combination with sulfanilamide or sulfapyridine give off substances which inhibit the bacteriostatic action of the chemical, but on dilution the bacteriostatic power returns. Peptone added to sulfanilamide has a similar effect, and the degree of inhibition of the bacteriostasis appears to depend on the concentration of the peptone and to

be independent (within limits) of the concentration of sulfanilamide. Dead streptococci added to human blood favor the growth of small implants of the same streptococci.

FROM AUTHOR'S SUMMARY. [ARCH. PATH.]

Metabolism; Infant Feeding; Milk and Other Foods

EFFECT OF FERRIC CHLORIDE ON THE UTILIZATION OF CALCIUM AND PHOSPHORUS IN THE ANIMAL BODY. PEGGY REHM and JET C. WINTERS, J. Nutrition **19**:213 (March) 1940.

The intake of food of two groups of rats was equalized so that the intake of minerals for both groups was the same. One group's diet was supplemented with enough ferric chloride to combine with one-half the phosphorus in the diet. A comparison of the amounts of total ash, calcium and phosphorus in the bodies of the rats showed that the group given the supplemented diet had a considerable reduction of the aforenamed minerals. Rehm and Winters thought that this result indicated that ferric chloride had a detrimental effect on the metabolism of calcium and phosphorus.

FREDEEN, Kansas City, Mo.

INDEPENDENCE OF THE ENDOGENOUS AND THE EXOGENOUS METABOLISM OF NITROGEN. E. WISE BURROUGHS, HELEN S. BURROUGHS and H. H. MITCHELL, J. Nutrition **19**:271 (March) 1940.

These investigators merely confirm the independence of the endogenous and the exogenous types of nitrogen metabolism. They tested thirteen individual amino acids, including all of those considered essential for growth, four amino acid mixtures and one complete protein mixture (egg) and obtained no evidence that these supplements depressed the endogenous metabolism.

FREDEEN, Kansas City, Mo.

RETENTION OF CALCIUM AND PHOSPHORUS BY PRE-SCHOOL CHILDREN. H. B. PIERCE, R. G. DAGGS, A. B. MESERVEY, W. J. SIMCOX, D. H. HOWE and M. W. FOOTE, J. Nutrition **19**:401 (April) 1940.

The object of this study was to determine whether the calcium of an alkaline salt mixture (calcium, sodium and iron phosphate) added to a wheat farina would be as well utilized by the preschool child as an equivalent amount of milk calcium.

The basal diet was planned so that milk would supply approximately 50 mg. of calcium per kilogram of body weight per day, or 80 per cent of the total ingested, and solid food the remainder. During experimental periods 200 mg. of milk calcium was replaced by 200 mg. of calcium in fortified cereal. Vitamin supplements were adequate.

The subjects were 4 girls and 6 boys ranging from 3 to 6 years. Each group consisted of 2 girls and 3 boys, and the sequence of diet periods was reversed. In one period the storage of calcium and phosphorus was definitely better when these two elements were supplied in part from the fortified cereal rather than from milk, while in a second period of comparison the availability of calcium and phosphorus was the same, as measured by retention.

The calcium, phosphorus and nitrogen balances were positive for all children throughout the study, and more phosphorus was stored than was required to convert retained calcium into bone. The daily storage of calcium was between 11 and 12 mg., and of phosphorus, between 7 and 8 mg., per kilogram of body weight. About 19 per cent of the calcium, and about 11 per cent of the phosphorus, was retained. Growth was better than average for all children. A daily intake of over 700 mg. of calcium was necessary for maximal retention of calcium. The utilization of calcium as measured by retention was equally good whether the source was milk or fortified cereal.

FREDEEN, Kansas City, Mo.

PRESENTING CERTIFIED MILK TO THE PROFESSION. SAMUEL ADAMS COHEN, New York State J. Med. **40**:20 (Jan. 1) 1940.

The advantages in the use of certified milk are cited. The production and distribution of certified milk automatically raises the standards of all other grades of milk. Methods for the production and standardization of goat's milk are being formulated.

AIKMAN, Rochester, N. Y.

Vitamins; Avitaminoses

THE VITAMIN A STATUS OF FAMILIES IN WIDELY DIFFERENT ECONOMIC LEVELS. PAULINE BEERY MACK and AGNES PAULINE SANDERS, Am. J. M. Sc. **199**:686 (May) 1940.

It was shown that there was a definite relationship between the average intake of vitamin A in the diet per person and the average response to photometer tests of members of 100 Pennsylvania families. Cash income, money spent for food and the education of adult members of the family have been shown to be related to the consumption of vitamin A by the family and to the consequent response of the members of the family to the photometer test.

Study points to the fact that many families, particularly those in the lower socioeconomic groups, are not selecting foods with a satisfactorily high content of vitamin A. The study indicates further that a larger estimated content of vitamin A in the diet per person may be needed than is generally recommended.

Good average responses to the photometer tests were associated not only with uniformly high intakes of vitamin A but with greater degrees of uniformity of response to the tests throughout the members of a certain family, a situation which is characteristic of biologic material in general, in which the greater the uniformity found, the more nearly is an optimum condition achieved with respect to a certain factor.

EMKE, Omaha.

THE RELATIONSHIP OF THE DIETARY INTAKE OF NICOTINIC ACID TO THE COENZYME I CONTENT OF BLOOD. ABRAHAM E. ALEXROD, EDGAR S. GORDON and CONRAD A. ELVEHJEM, Am. J. M. Sc. **199**:697 (May) 1940.

The results of the study on coenzyme 1 indicate that there is no diagnostic value in determinations in borderline cases of deficiency disease. The level of coenzyme 1 in the blood can be increased by the ingestion of large amounts of nicotinic acid, and the level of blood varies with the amount of nicotinic acid fed.

EMKE, Omaha.

CEREBRAL CARBOHYDRATE METABOLISM DURING DEFICIENCY OF VARIOUS MEMBERS OF THE VITAMIN B COMPLEX. H. E. HIMWICH, T. D. SPIES, J. F. FAZEKAS and SARAH NESIN, Am. J. M. Sc. **199**:849 (June) 1940.

Forty-nine observations were made on 27 polyavitaminotic patients, whose most significant deficiency disease was pellagra. Samples of blood entering and leaving the brain were examined for oxygen, sugar and lactic acid. The average arterial-venous differences for oxygen are 5.82 volumes per cent in this group, compared with 7.43 volumes per cent in normal subjects. For dextrose, the average arterial-venous difference was 7.6 mg. per hundred cubic centimeters, compared with 14.6 mg. per hundred cubic centimeters in normal subjects. No difference was observed in the average lactic acid content of arterial and venous blood.

A group of 7 persons with pellagra, presenting a clinical picture relatively uncomplicated by other deficiency diseases, revealed an oxygen arterial-venous difference of 6.16 volumes, per cent, somewhat lower than that for the normal person.

In 8 persons who had pellagra complicated by beriberi, a more marked depression of the oxygen arterial-venous difference was observed, with an average value of 4.69 volumes per cent. This difference may be caused either by an increase in

the blood flow to 60 per cent over the normal rate or by a diminution in cerebral metabolism. The latter possibility is regarded as more likely. If cerebral metabolism is decreased in pellagra complicated by beriberi, it is difficult to determine whether the low uptake of oxygen is due to lack of one vitamin or to polyavitaminosis. Such observations may afford a basis for an explanation of the mental changes noticed in patients with this syndrome.

EMKE, Omaha.

BERIBERI AND VITAMIN B_1 DEFICIENCY. EDWARD B. VEDDER, Am. J. Trop. Med. **20**:625 (Sept.) 1940.

The author discusses the numerous theories concerning the various deficiencies of vitamins that may be responsible for the lesions in the heart and nervous system and for the edema and serous effusions. He also discusses in detail the part pyruvic acid is thought to play in polyneuritis. The possibility that other vitamins than B_1 may play a part in beriberi is likewise discussed.

He concludes that further experimental study is necessary to prove or disprove the causation of the lesions of beriberi.

BURPEE, Augusta, Ga.

METABOLIC STUDIES AND THERAPY IN A CASE OF NEPHROCALCINOSIS WITH RICKETS AND DWARFISM. FULLER ALBRIGHT, WILLIAM V. CONSOLAZIO, FREDERICK S. COOMBS, HIRSH W. SULKOWITCH and JOHN H. TALBOTT, Bull. Johns Hopkins Hosp. **66**:7 (Jan.) 1940.

A girl of 13 had persistent rickets and dwarfism. The roentgenograms and the blood picture—normal serum calcium, low serum phosphorus, high serum phosphatase—indicated that the condition was rickets and not osteitis fibrosa. The condition was accompanied by massive deposits of calcium in the pyramids of the kidneys, hyperchloremia and a low level of the serum bicarbonate.

Tests for function of the kidneys showed only a moderate decrease of inulin clearance, markedly decreased ability to excrete chlorides and to make ammonia and a fixation of the specific gravity and the hydrogen ion concentration of the urine.

Therapeutic measures based on the results of metabolic studies were tried; they consisted of a diet low in salt content, only moderate amounts of vitamin D and a mixture of sodium citrate and citric acid. There resulted an extraordinary improvement of the bone disease. The therapy also led to a reestablishment of growth. It is suggested that the failure to grow may have been due to the acidosis.

LYTTLE, New York.

EFFECT OF COOKING UPON THE THIAMIN CONTENT OF FOODS. ELIZABETH AUGHEY and ESTHER PETERSON DANIEL, J. Nutrition **19**:285 (March) 1940.

The rat growth method was used to determine the losses of vitamin B_1 (thiamine) with different cooking procedures for a variety of foods. If the cooking water was discarded, the total losses in vegetables amounted to from 20 to 35 per cent. If sodium bicarbonate was added to green peas or snap beans, the destruction of the vitamin was markedly increased, but no loss was apparent in the thiamine content of boiled navy beans. The relative thiamine values of the different cooked foods and the daily human requirements for the vitamin were discussed.

FREDEEN, Kansas City, Mo.

THE ROLE OF VITAMIN K IN THE ETIOLOGY, PREVENTION AND TREATMENT OF HEMORRHAGE IN THE NEWBORN INFANT: PART II. W. W. WADDELL JR. and D. GUERRY III, J. Pediat. **15**:802 (Dec.) 1939.

Four cases of subclinical hemorrhagic disease, and 1 case of hemorrhagic disease of the usual variety associated with high prothrombin time are reported. In each instance the administration of vitamin K by mouth promptly reduced the prothrombin time to a safe and normal level and in the case of hemorrhagic disease controlled the bleeding. Synthetic vitamin K (menadione; 2-methyl-1, 4-

napthoquinone) was found to be equally effective in the treatment of 3 infants with high prothrombin time. A group of mothers were given 8 cc. of vitamin K and bile salts after the onset of labor. The prothrombin and the clotting time of the infants after delivery were studied and found to be lower in general than those of the control infants, though high prothrombin time occurred with too great a frequency to demonstrate any real effect of vitamin K. To another group of mothers vitamin K was given during the last two weeks of pregnancy. Though this group was a small one, the results were encouraging, and further similar studies may show that vitamin K used in a preventive way can materially lessen the incidence of intracranial hemorrhage associated with normal labor and delivery and of unnatural bleeding in the neonatal period. From their studies the authors are led to believe that there may be a seasonal incidence of deficiency of vitamin K.

RAUH, Cincinnati.

EFFECT OF VITAMIN C ON CREATINE AND CREATININE METABOLISM. CH'UAN FAN and THERESA T. WOO, Proc. Soc. Exper. Biol. & Med. **45**:90 (Oct.) 1940.

Administration of vitamin C to 4 normal subjects caused no increase in creatinuria. In a child with glycogen storage disease in whom it had been previously demonstrated that a decrease in creatine tolerance was present, administration of vitamin C produced a great increase in the urinary excretion of both creatine and creatinine. This was thought to be due to an increase in creatine formation in the body. No increase in urinary creatine was observed in a child with hypothyroidism after administration of ascorbic acid.

HANSEN, Minneapolis.

FORMATION OF THE ANTI EGG-WHITE-INJURY FACTOR (BIOTIN) IN THE RUMEN OF THE COW. L. W. MCELROY and T. H. JUKES, Proc. Soc. Exper. Biol. & Med. **45**:296 (Oct.) 1940.

Rumen taken from cows on a B-complex deficient diet protected chicks from dermatitis due to egg white injury, which indicates that the egg white injury factor (biotin) can be synthesized by the cow.

HANSEN, Minneapolis

MASSIVE DOSE THERAPY OF RICKETS. GEORGE OSKAR HARNAPP, Wien. klin. Wchnschr. **35**:698 (Aug. 30) 1940.

According to Harnapp, 12 to 15 mg. of vitamin D_2 in the form of a single oral dose is enough to cure rickets, even the severe osteomalacic type, in any case.

ABT, Chicago.

A STUDY OF THE ASPIRATED STERNAL BONE MARROW IN PELLAGRA. M. S. HWANG, P. T. KUO and W. SHIH, Chinese M. J. **58**:206 (Aug.) 1940.

The authors state that not enough attention has been paid to the study of the ultimate changes found in the bone marrow of pellagrins and that reports of such changes have been somewhat conflicting. A restudy of the myelograms from patients with this disease was made, and the results were tabulated. The majority of the 53 cases were studied before treatment and the remainder after the clinical use of nicotinic acid and diet. The ages of the patients were not listed.

A normal range was found for megaloblastic and erythroblastic cells, and the bone marrow characteristically indicated mild secondary anemia.

NEFF, Kansas City, Mo.

STUDIES ON THE REDOX POTENTIALS OF LIVING PIGEONS WITH AVITAMINOSIS B_1. T. ARAKI, Orient. J. Dis. Infants **26**:27 (July) 1939.

Using a specially devised potentiometer, the author measured the oxidation-reduction potentials of the subcutaneous tissues of living pigeons suffering with

avitaminosis B_1 and noted a gradual diminution in values with the progress of the deficiency. The maximal level of 85 millivolts was reached at the height of avitaminosis. The simultaneous measurement of the intact muscles of the same pigeons revealed the maximal reduction to be 105 millivolts. When vitamin B_1 was injected intravenously, the redox potentials increased, returning to the normal level within a few days. Inanition, which is frequently incriminated for various symptoms of avitaminosis B_1, has been found to exert no effect on potentiometric readings.

KATO, Chicago.

THREE CASES OF SCORBUTOID DEFICIENCY DISEASE IN BREAST-FED INFANTS: DOUBTFUL ROLE OF AVITAMINOSIS C. T. MAKI and E. KOJIMA, Acta pædiat. japon. **46**:507 (May) 1940.

The authors report the cases of 3 breast-fed infants who had marked enlargement of the costochondral and knee joints, attended by great pain in these areas. Two were boys, 23 and 19 days old respectively, and the third was a girl 17 days old. There was no history of dietary deficiency of the mothers and no abnormal diminution in the vitamin C content of the milk, blood or urine. The therapeutic effect of administration of vitamin C to these babies was both prompt and definite. For these reasons, the scorbutoid condition seen in such patients must be on an entirely different basis from that observed in artificially fed infants.

KATO, Chicago.

THE VITAMIN C CONTENT OF DIET IN BARLOW'S DISEASE. T. SUGITA, Acta pædiat. japon. **46**:552 (May) 1940.

In the author's experience the average intake of vitamin C of the breast-fed infant is from 15 to 30 mg. daily, or about 6 mg. per kilogram of body weight, while that of the artificially fed infant is always lower. In 21 cases of malnutrition, Sugita found the daily intake to be less than 14 mg. in 47 per cent; no infant took over 28 mg. In 29 cases of infantile scurvy, the daily intake of vitamin C prior to hospitalization was 14 mg. or less. Satisfactory cure in 35 cases of Barlow's disease was effected with l-ascorbic acid in doses varying from 39 to 115 mg. daily, given by parenteral injection, and in over 50 per cent of the cases clinical improvement was noted in an average of seven days.

KATO, Chicago.

PARALLEL INVESTIGATIONS INTO THE ASCORBIC ACID CONTENT IN THE BLOOD PLASMA AND INTO THE STRENGTH OF THE CUTANEOUS CAPILLARIES IN HEALTHY CHILDREN. N. G. AHLBORG and G. BRANTE, Acta med. Scandinav. **104**:527, 1940.

For 61 healthy elementary school children of Uppsala the capillary fragility and the vitamin C content of the plasma were determined. A correlation coefficient of 0.57 ± 0.09 was found. The capillary fragility test and the vitamin C content of the plasma were followed in 1 subject who had extremely low vitamin C content in the plasma and who subsequently received 100 mg. of ascorbic acid by mouth daily. While the plasma showed a good vitamin C level in nine days, the capillary fragility did not return to normal until the twenty-sixth day. Six subjects with subnormal nutrition who showed increased capillary fragility received 100 mg. of vitamin C daily for fifteen days. The capillary fragility and the vitamin C content of the plasma were normal fifteen days after the last dose.

KAJDI, Baltimore.

STUDIES ON ROENTGENOGRAPHIC CHANGES IN BONES AS AN EARLY SIGN OF SCURVY IN INFANTS. P. BRAESTRUP and S. A. CHROM, Acta pædiat. **27**:63, 1939.

Roentgen examination of the skeletons of 25 infants with extremely low concentrations of ascorbic acid in the blood failed to reveal the changes described

by Park, Guild, Jackson and Bond as forerunners of scurvy, thereby confirming the conclusion of these authors that no reliable early clinical sign of scurvy exists.

McCUNE, New York.

INVESTIGATION OF THE ASCORBIC ACID EXCRETION IN THE URINE OF HEALTHY AND FEBRILE CHILDREN. A. GÖRTZ, Acta pædiat. **27**:429, 1940.

In 1938 Lund demonstrated that ascorbic acid is a threshold substance which does not appear in the urine until the concentration in the blood is 0.8 mg. per hundred cubic centimeters. Other investigators have made observations which suggest that the renal threshold is lowered during febrile diseases. To throw light on this point the author conducted an inquiry into the threshold level for ascorbic acid in 16 afebrile children, 6 children suffering from trivial infections and 6 children with pneumonia. The following generalizations are made: The renal threshold for ascorbic acid is reduced in patients suffering from pneumonia but never so much lowered as to cause a significant loss of vitamin C. The absolute level of the threshold is proportional to the concentration of ascorbic acid in the blood, low blood levels being associated with low threshold values and vice versa. Artificial increase of the blood concentration of ascorbic acid was found to result in elevation of the renal threshold.

McCUNE, New York.

HYPOPHYSIAL NANISM RESULTING FROM CRANIOPHARYNGIOMA, E. GJÖRUP, Acta pædiat. **27**:508, 1940.

A 20 year old woman gave a history of attacks of headache from early childhood until an issue of fluid from her nose and mouth brought relief at the age of 8 years; the pain had seemed to center over the right eye and had been attended by some flickering of vision. Growth ceased when she was 12 years old; somatic maturity failed to make its appearance. Estrogen treatment was unsuccessful in initiating menstruation. Polydipsia, polyuria and loss of visual acuity had not been noted. At 20 years of age the patient was only 135 cm. in height; although the body proportions were appropriate to the chonologic age, the secondary sex characters were virtually absent. The basal metabolic rate was 66 per cent of normal; the value for fasting blood sugar was approximately 80 mg. per hundred cubic centimeters. Roentgen examination of the hands and feet showed the epiphysial lines to be partially preserved, again a feature appropriate to the chronologic age. Roentgenograms of the skull revealed a mass of material of the density of calcium, occupying a position immediately above the sella turcica; the outlines of the sella were not greatly disturbed. Examination of the eyes showed the optic nerves to be only slightly compromised. A diagnosis of calcified craniopharyngioma appeared obvious. Since the cyst had previously evacuated itself spontaneously, surgical intervention was delayed until such time as visual symptoms or manifestations of increase of intracranial pressure might demand it.

The paper contains a brief synopsis of intracranial tumors in children, with particular attention to the incidence of craniopharyngiomas.

McCUNE, New York.

Hygiene; Growth and Nutrition; Public Health

DEVELOPMENTAL GROWTH OF THE FACE IN RELATION TO THE DENTURE. LEONARD P. WAHL, Am. J. Orthodont. **25**:234 (March) 1940.

A conception of some of the knowledge gleaned from research and investigations on the interrelation of the growth and development of the face and the denture is presented. The works of Angle, Hellman, Broadbent, Brodie, Todd, John Hunter, Brash and others are quoted.

LEWIS, Dayton. [ANGLE ORTHODONTIST.]

A Plastic and Graphic Technique for Recording Dental Changes and Facial Growth. Herbert I. Margolis, Am. J. Orthodontics **25**:1027 (Nov.) 1939.

This is the first of a series of articles on facial growth and changes and a manner in which to record such changes. A standardized technic for stereoscopic photography is described in detail. Margolis believes the orthodontist should think in terms of three-dimensional records, since his work is moving teeth in space.

Lewis, Dayton. [Angle Orthodontist.]

Motor Performance in Adolescence, Including the Study of Relationships with Measures of Physical Growth and Maturity. Anna Espenschade, Monograph of the Society for Research in Child Development, 1940, series no. 24, vol. 5, no. 1.

During the years from 1934 to 1938 seriatim measurements of gross motor performance were made on the girls and boys of the adolescent study group of the Institute of Child Welfare of the University of California. Motor performance was considered directly dependent on the development of certain abilities within the person, especially coordination, strength, speed and accuracy. The measurement of gross motor performance, then, was designed to sample these abilities. Six tests were given, and the results were analyzed in terms of their reliability, validity and consistency with the results of repeated tests. It was shown that with few exceptions the data were consistent and as reliable as could be expected in tests of this nature. While adequate to portray trends of growth the measures were not sufficiently reliable for the determination of short term changes in the rate of growth during the adolescent period.

The intercorrelations of motor performances were all positive but varied greatly in extent. In general, gross motor performances were more closely related to each other than to fine motor performances. The correlation structure at all ages was similar in the two sexes, but performances were somewhat less specialized in girls than in boys and in younger than in older children.

Growth in ability to perform motor acts appeared to reach its maximum at approximately 14 years of age in girls but continued in boys through the seventeenth year. At the same time there were wide individual differences in rate of growth and in levels of ability. Sex differences were apparent at all ages studied but were greater in older than in younger children.

The correlations between motor performances of girls and all measures of physical growth and maturity were low and in most cases not statistically significant. Motor performances of boys, on the other hand, were positively and significantly related to measures of maturity—chronologic, anatomic and physiologic. These observations were interpreted in terms of sex differences in level of maturity. There was some tendency for the correlations between motor performances of boys and anthropometric measures to decline with age. Measures of strength were substantially related to gross motor performance in boys but only slightly related in girls. The degree of relationship of these factors in the two sexes became more comparable when the height, weight and physiologic maturity of boys were held constant.

Case studies are presented to illustrate the consistency of individual position in the group and to show the influence of specific factors on motor performances.

Espenschade, Berkeley, Calif.

Exercise of Children and Adolescents. Pierre Nobécourt, Gaz. d. hôp. **112**: 1369 (Nov. 8) 1939.

This is merely a medical school lecture, containing no new observation or suggestion which would repay one for reading it.

Kajdi, Baltimore.

PHYSICAL CULTURE AND ATHLETICS FOR CHILDREN AS VIEWED BY A PEDIATRICIAN. C. NOEGGERATH, Rev. franç. de pédiat. **15**:293, 1939.

The author gives an exceedingly instructive exposition of the types of exercise suitable to different age periods of childhood. His conclusions are based on his understanding of the muscular, cardiac, respiratory and neurophysiologic aspects of these age periods. The heart of the infant or the young child cannot significantly increase its output, particularly for any long period. For the infant spontaneous movement suffices; for the young child exercise should be in the form of play, with frequent periods of rest. The shoulder girdle is weak, and the flexor muscles are already stronger than the extensor muscles, so that swinging or hauling by the arms should not be indulged in. For the older group as well, specialization in play or exercise is inadvisable, as it does not tend to produce well rounded development.

LESLIE, Evanston, Ill.

PUERICULTURE. F. FERRARO, Med. inf., Rome **11**:9 (Jan.) 1940.

Quoting a Fascist proverb of Mussolini, "Arms alone will not give victory unless the man really wishes to obtain it," a plea is made to Italians to prevent Italy from becoming a decadent nation as it seems possible the nation may if the birth rate continues to decline. Even illegitimate children, it is urged, must receive the best of care, and the unfortunate mothers enabled to nurse and give good care to their infants. Much advice is given to those who are supervising the health of young children.

This article is a lecture given in a course on the improvement of health in Italy.

HIGGINS, Boston.

PARASITISM IN THE ORGANIZATIONS OF SOCIAL ASSISTANCE: HOW TO AVOID IT. YETTY VAN LITH DE LUNGE, Bol. Inst. internac. am. de protec. a la infancia **13**:836 (April) 1940.

This is a plea for a central general register for organizations of social assistance in Chile. The hope is that fraud and duplicity may be avoided and that organizations which exist for their own aggrandizement rather than for the good of the community may be done away with. The present government of Chile is in favor of such a coordination.

LESLIE, Evanston, Ill.

GROWTH AND DEVELOPMENT OF CHINESE INFANTS OF HUNAN: I. BODY WEIGHT, STANDING HEIGHT AND SITTING HEIGHT DURING FIRST YEAR. T. F. SU and C. J. LIANG, Chinese M. J. **58**:104 (July) 1940.

The authors write of their observations in two well baby clinics in China and present the statistical data according to sex and age. The values for growth are generally the same as those reported from Peiping but higher than the figures from Tsinan and Shanghai. They are not so high as those for American infants reported by the Iowa Child Welfare Research Station. It was seen that the trunk grows more slowly than the extremities in the first twelve months. The curves of growth follow those of body weight.

NEFF, Kansas City, Mo.

THE DEVELOPMENTAL PROPORTIONS OF FINNISH SCHOOL CHILDREN. A. RUOTSALAINEN, Acta pædiat. **27**:374, 1940.

Measurements of the body proportions of several thousand Finnish school children are tabulated and discussed. In keeping with the experience in other nations, both the stature and the weight of children of the present generation are greater than those of their forebears.

MCCUNE, New York.

Prematurity and Congenital Deformities

A Study of the Heredity of the Anomalies of the Jaws. O. Rubbrecht, Am. J. Orthodontics **25**:751 (Aug.) 1939.

The author concludes that the shape and size of the jaws are in a great measure determined by heredity and consequently that endognathism and exognathism are dependent to a great extent on heredity. Various and numerous family pedigrees are shown and illustrated with photographs and casts.

Lewis, Dayton. [Angle Orthodontist.]

Some Facts About Premature Infants. Charles Tarleton Williams, New Orleans M. & S. J. **93**:244 (Nov.) 1940.

The author gives the results of an analysis of data on 100 premature infants who had been followed for ten years after birth.

He finds that nearly all premature children are handicapped for their first two years. Those who do well at the beginning usually suffer no mental or physical handicap in later years, while those who do poorly are more likely to have such handicaps.

Three per cent premature children showed mental deficiencies, in every instance associated with maternal toxemia of pregnancy. Infants showing immaturity were especially prone to do poorly.

Berkley, Los Angeles.

Maternal Age, Order of Birth and Developmental Abnormalities. L. S. Penrose, J. Ment. Sc. **85**:1141 (Nov.) 1939.

Penrose found that the mean age of the mothers of 224 mongolian idiots was 37.4. The mean age of the mothers of 1,132 children with mental defects other than mongolian idiocy was 29.4. The probability that a mother will have a mongolian idiot is more than doubled for every increase of 5 years after the age of 25. The same applies to anencephaly, hydrocephaly and spina bifida. The mothers of 441 children with congenital defects and malformations had a mean age of 31.7. Maternal age is also an important factor in placenta praevia centralis. Congenital pyloric stenosis is more apt to occur in the first born.

Kasanin, San Francisco. [Arch. Neurol. & Psychiat.]

Malformation of the Face and Jaws in Craniofacial Dysostosis. Pierre de Gunten, Rev. de stomatol. **41**:611 (Aug.) 1939.

On making a detailed study of the malformations of the face and jaws of 5 patients, the author concludes that the malformations may be classed in the syndrome of craniofacial dysostosis. Atrophy of the maxillas is the most constant morphologic character. It is very marked and always symmetric. The mandible is essentially normal; the teeth show irregularity (this is always symmetric), and open bite is frequent. The author lays the deformity and singular facial configuration of these patients to the atrophy of the maxillas.

Newcomb, Cleveland. [Angle Orthodontist]

Bringing-Up of the Immature Infant. I. Nasso, Med. inf., Rome **11**:1 (Jan.) 1940.

History tells us that such prominent persons as Newton, Darwin, Napoleon, Hugo, Rousseau, Voltaire and Lamartine began life as immature infants.

The Italian government has been particularly interested in formulating and promulgating the most helpful advice possible on the proper rearing of immature infants.

Whereas any acute or chronic illness may be responsible for immaturity, syphilis and tuberculosis are the most prominent causes. Unusual incidents of birth, as

twinning and obstetric difficulties are frequent causes. The explanations of many cases of immaturity cannot be well established.

Effective treatment of immature infants includes proper nursing, satisfactory nutrition, including mother's milk and vitamins, and indicated glandular therapy.

HIGGINS, Boston.

A CASE OF SITUS INVERSUS VISCERUM WITH CONGENITAL MALFORMATION OF THE HEART (BILOCULAR HEART). A. CALAMARI, Pediatria **47**:989 (Nov.) 1939.

The case of a 4 month old infant is described. The clinical and autopsy observations are reported. Besides the situs inversus viscerum there was a congenital malformation of the heart. There was absence of the interatrial and interventricular septum. The circulation of the blood is reconstructed from the aforementioned observations. The auricles and the ventricles appeared as one without their septums. The valves were normal in their development. The pulmonary artery originated from the left ventricle. The trunk of the aorta originated from the right ventricle. There were three aortic semilunar valves, one anterior and two posterior, in contrast to the normal arrangement (two anterior and one posterior).

MARTOCCIO, Utica, N. Y.

Newborn

THE NATURE OF THE HEMORRHAGIC DISEASE OF THE NEWBORN: DELAYED RESTORATION OF THE PROTHROMBIN LEVEL. ARMAND J. QUICK and ARTHUR M. GROSSMAN, Am. J. M. Sc. **199**:1 (Jan.) 1940.

The authors show that the concentration of prothrombin in the blood of infants at birth is relatively high, about 60 to 75 per cent of the normal adult level, but often drops abruptly during the first few days of life and is restored spontaneously and usually promptly to normal. The suggestion is made that the recovery of the concentration of prothrombin is brought about by the establishment of bacterial flora in the intestines and that this initiates the synthesis of vitamin K which becomes available to the organism of the infant for the production of prothrombin.

The hypothesis is presented that hemorrhagic disease of the newborn is due to delayed restoration of the prothrombin level. It is recognized clinically by external or internal bleeding and is characterized by an exceedingly low concentration of prothrombin in the blood. It is usually self limited but may be fatal. It is promptly cured by oral administration of vitamin K.

HENSKE, Omaha.

BLOOD STUDIES ON THE NEWBORN: II. DIRECT AND TOTAL BLOOD BILIRUBIN: DETERMINATION OVER A NINE-DAY PERIOD WITH SPECIAL REFERENCE TO ICTERUS NEONATORUM. T. R. WAUGH, FREDERICK T. MERCHANT and GEORGE B. MAUGHAN, Am. J. M. Sc. **199**:9 (Jan.) 1940.

The results in two hundred and fifty bilirubin determinations on newborn infants during the first nine days of life demonstrate a state of hyperbilirubinemia at birth which increases during the first four days and then falls toward normal. Icterus neonatorum developed in 30 per cent of the newborn infants examined. In clinical icterus with the degree of hyperbilirubinemia, icterus was reported when the level of total bilirubin reached 5 mg. per hundred cubic centimeters or more. There were cases reported with lower blood values, as well as cases with figures above this level, in which icterus was apparently absent.

The authors sought to determine the existence of any relationship between the amount of blood destruction taking place during the first few days of life, the degree of hyperbilirubinemia and the development of icterus neonatorum. It was shown that there is a continuous fall in hemoglobin and in volume of packed red cells throughout the period studied, while the bilirubinemia reaches its highest level on or about the fourth day and then declines toward normal. No relationship

exists between the individual total fall in hemoglobin and volume of packed red cells and the amount of bilirubinemia during the nine days studied. It was shown that the resistance of erythrocytes was increased during the study and that variations in the index of hemolysis in normal infants have no effect on the degree of hyperbilirubinemia which develops. The studies on the relationship of blood destruction and fragility of the erythrocytes to the degree of bilirubinemia show no difference in this respect between the icteric and the nonicteric infants. The authors therefore take the view that hyperbilirubinemia in general and icterus neonatorum in particular are made possible by the increased destruction of blood which is obviously taking place during the first few days of life. Whether sufficient bilirubinemia develops to cause the infant to exhibit clinical icterus is dependent on the ability of the cells of the liver to excrete bilirubin.

HENSKE, Omaha.

GONOCOCCIC ARTHRITIS OF THE NEWBORN TREATED WITH SULFANILAMIDE. PAUL P. PARRISH, WILLIAM A. CONSOLE and JOSEPH BATTAGLIA, J. A. M. A. **114**:241 (Jan. 20) 1940.

A 3½ week old baby whose parents had evidence of acute gonorrhea before and at the time of her birth presented a swollen and painful knee joint which proved on aspiration to be infected with gonococci. There was no evidence of a portal of entry. About two weeks of treatment with sulfanilamide, 1 to 3 grains (0.06 to 0.19 Gm.) per pound of body weight, relieved the condition. Four days more of treatment relieved a recurrence.

The literature is reviewed, presenting 87 cases with a mortality of 20 per cent. Sulfanilamide appears to offer a better outlook for cure and absence of sequelae.

HEERSMA, Kalamazoo, Mich.

NEUROLOGICAL SEQUELAE OF KERNICTERUS. G. M. FITZGERALD, J. G. GREENFIELD and B. KOUNINE, Brain **62**:292, 1939.

Kernicterus is a disease the acute phase of which is a well recognized clinical entity. It frequently affects several children in the same family. The child is normal at birth, but within the first three days shows severe jaundice. Within twenty-four hours there is evidence of involvement of the nervous system, characterized by tonic and clonic movements, hypertonia and opisthotonos. Children affected usually die within five days. Pathologic examination in cases of the acute phase reveals that certain nuclei of the brain are specifically involved. These areas are stained deep yellow, and the cells in the pigmented areas are glassy and homogeneous, with a tendency toward cytolysis. The structures most frequently affected, in the order of severity, are the subthalamic nuclei, the basal ganglions, the cornu ammonis, the inferior olive, the dentate nucleus, the thalamus and some nuclei of the cranial nerves in the medulla. The jaundice has been variously attributed to a blood dyscrasia with increased destruction of blood elements, to intoxication of hepatic origin, to fetal septicemia and to maternal toxemia. The first of these causes seems most probable.

The specific localization of the destructive process in the brain appears to depend on some characteristic of the cells or of the blood supply of specific areas. Experimentally it has been shown that areas of the brain which normally contain iron are most susceptible to anemia, from whatever cause, and to intoxication from bile pigment or manganese. It is suggested that in kernicterus the primary factor is maldevelopment of some degree, while the localization depends on the relative ischemia of the affected areas.

A few cases have been reported in which the patients survived the acute phase of kernicterus. The authors report 3 such cases, in 2 of which there were pathologic studies. The essential features were identical in all the cases. There was a history of severe neonatal jaundice, and in many cases several siblings were affected. The onset of jaundice was followed rapidly by such nervous symptoms as tonic and clonic movements, rigidity and opisthotonos, alternating

with flaccidity. Later, and usually within the first four weeks, choreoathetoid movements appeared. As the child grew older, there developed emotional instability, mental retardation and inability to hold up the head. Pathologically, the same regions observed to be pigmented in the acute stage of kernicterus were involved in the chronic. In the more affected areas loss of ganglion cells and demyelination have been consistently observed.

In view of the anatomic similarity of kernicterus and such disorders as Wilson's disease, Hallervorden-Spatz disease and idiopathic forms of dystonia musculorum deformans in children, it seems important in cases of disorders of the latter group to seek carefully for neonatal jaundice as a possible etiologic factor.

MASLAND, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

COLLODION DISEASE. M. COFFIN, Bull. Soc. pédiat. de Paris **37**:337 (June) 1939.

A newborn boy presented a shiny, smooth surface of the skin which is described "as if he were dipped in collodion." Desquamation in sheets occurred. The skin later took on a normal appearance. There was no erythroderma. The infant developed normally.

BENJAMIN, Montreal, Canada.

Acute Contagious Diseases

A SKIN TEST FOR SUSCEPTIBILITY TO PERTUSSIS. L. P. STREAN, Canad. M. A. J. **42**:525 (June) 1940.

The endotoxin used in the test for susceptibility to whooping cough is stable over a period of months and produces positive skin reactions by the virtue of its primary toxicity.

While the trial of the endotoxin at the Children's Memorial Hospital was carried out on a comparatively small group, the correlation noted in those immune to the disease indicates a high degree of specificity.

The test must be watched carefully between the sixth and twenty-fourth hours, as the erythema which develops, measuring from 1 to 3 cm. in diameter, may come on early and fade rapidly, or may be delayed and not show up for twenty-four hours.

This test appears to bear the same relationship to whooping cough as the Schick test does to diphtheria.

The possibility of establishing immunity by the use of an endotoxoid is suggested.

MOORE, Omaha.

COMMUNICABLE DISEASES AND THE SCHOOL. ERNEST L. STEBBINS, New York State J. Med. **39**:2174 (Dec. 1) 1939.

Since in over 50 per cent of the reported cases of scarlet fever, whooping cough, measles and diphtheria the patients are children between the ages of 5 and 14 years, the school authorities are considerably concerned regarding the prevention of such diseases. The closest cooperation is necessary between the practicing physician, the school physician, the school authorities, the school nurse and the health officer if the best results are to be obtained. The recognition of diseases in the schools and methods of administering school immunization programs are especially stressed.

AIKMAN, Rochester, N. Y.

ANTERIOR POLIOMYELITIS (RELATION TO HYPERTENSION IN YOUNG ADULTS). HARRY DAN VICKERS, New York State J. Med. **40**:55 (Jan. 1) 1940.

Vickers reports arterial hypertension in 3 patients, aged 28, 25 and 31 years respectively, who had had anterior poliomyelitis in childhood. Blood pressure readings were taken on several others known to have had poliomyelitis, and the pressure was found to be elevated. The subject warrants further study.

AIKMAN, Rochester, N. Y.

PREVALENCE OF POLIOMYELITIS IN THE UNITED STATES IN 1939. C. C. DAUER, Pub. Health Rep. **55**:955 (May 31) 1940.

In 1939, 7,331 cases of poliomyelitis were reported—a rate of 5.6 per million of population. Four states reported a rate of 20 or over: New Mexico, South Carolina, Arizona, Minnesota. Three states reported a rate between 15 and 20: Michigan, Utah, California. Fifteen states had a rate in excess of the maximum of 4.3 reported for 1938. There was also a marked variation in age reported; in South Carolina 68 per cent of the patients were under 5 years of age, while in New York only 14 per cent were. The case fatality rates were low and varied between 2.5 and 9 per cent.

SANFORD, Chicago.

SUMMARY OF CURRENT PREVALENCE OF COMMUNICABLE DISEASE. Pub. Health Rep. **55**:1003 (June 7) 1940.

For the period of April 21 to May 18, 1940, the incidence of every communicable disease except influenza was below the median for the years 1935 to 1939. Influenza was 15 per cent above the median, with an excess of cases in the South Atlantic and West South Central regions. The incidence of diphtheria was the lowest on record for this period. The average mortality from all causes was 11.4 per thousand inhabitants, which is 0.4 lower than the average.

SANFORD, Chicago.

ADRENALIN CONTENT OF THE ADRENAL GLANDS IN DIPHTHERIA INTOXICATION. C. A. ASHFORD, Brit. J. Exper. Path. **20**:385, 1939.

Ashford has estimated the epinephrine content of the adrenal glands in diphtheria intoxication to determine whether the content is reduced during the acute stages of diphtheritic toxemia. Reports on this point, based mainly on histologic methods applied to experimental animals and human postmortem material, have been conflicting, and a number of theories of the circulatory collapse have been built up on the assumption of a depletion or an exhaustion of the medullary epinephrine. Guinea pigs have been used, and the results show that reduction of epinephrine content to any marked extent is not found. Histologic observations are reported briefly, and the possible significance of cortical damage is discussed.

[ARCH. PATH.]

THE NUTRITION OF CORYNEBACTERIUM DIPHTHERIAE. W. C. EVANS, W. R. C. HANDLEY and F. C. HAPPOLD, Brit. J. Exper. Path. **20**:396, 1939.

Evans, Handley and Happold, continuing their studies on the nutritional requirements of Corynebacterium diphtheriae types, find that the additional growth factor present in tissue extractives required by certain gravis strains is pantothenic acid. The mitis and some gravis strains which had previously been grown in chemically defined mediums synthesize this "gravis growth factor." Pantothenic acid is a compound of beta-alanine and a dihydroxyvaleric acid; according to current literature this substance is identical with the chick antidermatitis factor and is one of the B complex vitamins. The paper also describes experiments which show that strains of C. diphtheriae grown in chemically defined mediums synthesize substances with physiologic activities similar to those of aneurin, riboflavin and "co-enzymes I or II."

[ARCH. PATH.]

SCHICK IMMUNITY AFTER ACTIVE IMMUNIZATION COMPARED WITH THAT FOLLOWING DIPHTHERIA. JOHN F. WARIN, Brit. M. J. **1**:655 (April 20) 1940.

A comparison was made between two groups of children, one having been immunized by artificial means and the other tested for immunity after an attack of diphtheria. The author's conclusion is that a group of elementary school children had gained better through immunization, as judged by the Schick test, than that obtained by a comparable group of children who had passed through an attack of diphtheria.

ROYSTER, University, Va.

DIPHTHERIA PROPHYLAXIS: OPTIMUM DOSAGE AND TECHNIQUE IN USE OF ALUM-PRECIPITATED TOXOID. J. TUDOR LEWIS, Brit. M. J. **1**:728 (May 4) 1940.

Lewis states that alum-precipitated diphtheria toxoid is the preparation of choice. Sixteen months after immunization with alum-precipitated toxoid, studies were made on the blood of 49 children, with titrations of antitoxin. The summary of the article follows:

"The results are given of antitoxin titrations in forty-nine children who were bled sixteen months after 0.1 c.cm. of A.P.T. followed in two weeks by 0.5 c.cm.

"It is shown that sixteen months after A.P.T. administered in this fashion at least 10 per cent of children may be susceptible to a large dose of virulent organisms.

"Certain modifications in dosage and technique are advocated as a means of increasing the antigenic effect without increasing the number of injections. It is suggested that this procedure may with advantage be adopted by all scheme-making authorities."

ROYSTER, University, Va.

NOTES ON RUBELLA WITH SPECIAL REFERENCE TO CERTAIN RHEUMATIC SEQUELAE. R. A. BENNETT and W. S. C. COPEMAN, Brit. M. J. **1**:924 (June 8) 1940.

An epidemic of rubella occurring in February and March 1940 is described, with more than 300 cases observed. The onset and course in a number of these cases were irregular and unusual. Complications are described and relapses mentioned. A summary is as follows:

"In a recent epidemic of rubella certain deviations from the normal were observed. These are described, and concern the onset, course and complications of the disease. Certain cases of relapse are also described and commented upon.

"The most important complication described is the occurrence of 'rheumatic' conditions of varying degrees of severity. These ranged from transient joint and muscle pains to severe lumbago and sciatica, for which the sufferers had to be hospitalized. Three cases also occurred that were clinically indistinguishable from rheumatic fever. One of these is described in detail.

"Other unusual complications observed frequently were severe pains in the gums; tonsillitis, which appeared to be severe but of which the victim seemed to be almost unaware; and an intense degree of desquamation, occurring within a few hours of the rash having faded. Generalized adenitis with a temporarily abnormal blood count showing leukopenia with relative lymphocytosis was not infrequent, whilst a secondary rise of temperature forty-eight hours after defervescence with a recurrence of constitutional symptoms was also noticed in a considerable number of cases."

ROYSTER, University, Va.

PRELIMINARY OBSERVATIONS ON THE USE OF CONVALESCENT SERUM IN THE TREATMENT OF ACUTE RHEUMATISM. C. A. GREEN, A. J. GLAZEBROOK, S. THOMSON and W. A. HOPKINS, Proc. Roy. Soc. Med. **33**:275 (March) 1940.

A considerable amount of acute rheumatism was found in young men in a certain training establishment. The attack in the majority of cases was antedated by nasopharyngeal infection. In a few cases the disease appeared with a dramatic onset of hyperpyrexia, sweating and polyarthritis. The initial pyrexia seldom lasted longer than one week, irrespective of the treatment adopted. Relapses occurred frequently, but cardiac symptoms were rare. As these patients were otherwise healthy adults, it was decided that serum taken from them during convalescence should be tried in the more acute phases of the disease in subsequent cases. The method of preparation of the serum is described briefly. It was given either muscularly or intravenously in doses of 10 to 20 cc. It was used in the treatment of 15 patients, 10 of them receiving no additional treatment. Histories of all 15 cases and comments on them are given in the report. It was found that when the serum was given in the early stages of an attack, especially in primary attacks, the period of pyrexia was reduced, and there was no doubt that arthritic

pain was relieved. Two of the patients showed partial collapse within a short period after receiving an injection of the serum but rallied in a few minutes on receiving epinephrine and oxygen.

WILLIAMSON, New Orleans.

MEDIASTINAL AND SUBCUTANEOUS EMPHYSEMA DURING THE COURSE OF MEASLES. R. A. MARQUÉZY, LADET, PERROT and VIALATTE, Bull. Soc. pédiat. de Paris **37**:294 (June) 1939.

In a 17 year old boy, mediastinal and subcutaneous emphysema developed on the second day after the appearance of a measles rash. He had marked tracheobronchitis. Recovery ensued. Emphysema occurred in a boy 3 years old on the thirteenth day after the onset of severe measles. Sudden collapse and dyspnea accompanied the appearance of the emphysema. Rapid improvement of the child's condition took place, and roentgenographic examination nine days later showed complete clearing of the emphysema.

BENJAMIN, Montreal, Canada.

STRYCHNINE THERAPY IN SEVERE DIPHTHERIA. A. SABELLI and L. RODRIGUEZ GAETE, Arch. argent. de pediat. **11**:36 (Jan.) 1939.

The authors advise the use of strychnine in addition to serum in the treatment of severe diphtheria. Strychnine is used in the dosage of 0.5 to 1 mg. per kilogram of body weight. During the first few days it should be injected subcutaneously every three hours; later it may be given orally. Strychnine sulfate is the preparation used.

The treatment should be continued until clinical or electrocardiographic examination indicates improvement.

SCHLUTZ, Chicago.

THE PROPHYLAXIS OF MEASLES THROUGH THE USE OF PLACENTAL GLOBULIN. H. PUMARINO F., Rev. chilena de pediat. **10**:725 (Nov.) 1939.

Pumarino advises the use of placental globulin in proper dosage during the first days of the contagion. He finds placental globulin entirely safe. It is readily obtained in any amount and is easily preserved. As a prophylactic measure against measles, the administration of this substance is superior in the author's opinion to all other measures. It may prevent measles and will certainly produce attenuation of the attack.

SCHLUTZ, Chicago.

CLINICAL STUDY OF THE DISEASES OF THE KIDNEY IN SCARLET FEVER. WALTER NEU, Zentralbl. f. inn. Med. **60**:577 (July 29); 593 (Aug. 5) 1939.

According to Vollhard's classification, two types of nephritis occurring in conjunction with scarlet fever should be distinguished:

1. Intrainfectious glomerulonephritis, occurring during the beginning of the infection and characterized by foci in several glomeruli. The principal symptoms are albuminuria, cylindruria, hematuria and rise in blood pressure. A special subtype of this intrainfectious nephritis is the interstitial nephritis; it is seen in the septic course of scarlet fever.

2. Postinfectious acute glomerulonephritis.

Between 1927 and 1937, 1,845 children suffering from scarlet fever were observed. Of these, 944 (51 per cent) showed no complications; 200 (10.8 per cent) had complications, but none involving the kidneys; 194 (10.4 per cent) had febrile albuminuria without nephritis; in 44 (2.3 per cent) acute diffuse glomerulonephritis developed. Two of these 44 patients showed a general septic scarlet fever and succumbed. All the other patients recovered fully, without showing any sequelae on later examination. Glomerulonephritis developed no more frequently in children suffering from albuminuria in the onset of scarlet fever than in the other children. During the third week of scarlet fever, in 107 patients (6.3 per cent) mild albuminuria or hematuria or elevated blood pressure and insufficient

diuresis were recorded. However, these symptoms were not regarded as sufficient to warrant the diagnosis of acute glomerulonephritis.

Focal intrainfectious glomerulonephritis was observed in 245 patients (13.2 per cent). All the focal infections were mild and subsided during the course of scarlet fever.

In 5 patients interstitial nephritis was seen. This is the most rare complication of scarlet fever. In all instances it occurred with septic scarlet fever. The children succumbed either from the sepsis or from uremia. But 1 child presented acute glomerulonephritis combined with interstitial nephritis and died in uremia.

ARON, Chicago.

Acute Infectious Diseases

FACTORS IN THE DIAGNOSIS OF INTESTINAL PROTOZOA IN MAN AND IN THE INTERPRETATION OF THE FINDINGS. JAMES L. BERLAND, Am. J. Digest. Dis. **7**:401 (Oct.) 1940.

The author stresses the following points: 1. The necessity of proper collection of material in examination for intestinal protozoa. Saline purges with examination of the liquid stools while warm offers the best chance to recover both cysts and active Endamoeba. Proctoscopic examination is often a great help. The incidence of recovery of Endamoeba is very small when a hard firm stool is examined. Material may be rendered unfit for examination by improper collection or by giving the examinee oil, barium sulfate or a bismuth compound.

2. The incidence of intestinal protozoal infection in all parts of the United States is such that each physician is confronted frequently by infected persons.

3. The exact relation of these parasites to the host is not yet proved.

4. Proper statistical evaluation of protozoal infection and assay of the part played by a protozoan in the symptomatology of a patient depend on compensation for the fact that protozoa are not present daily in the stool of infected persons.

MORRISON, Savannah, Ga.

RHEUMATIC HEART DISEASE IN ADOLESCENCE. R. R. STRUTHERS, Canad. M. A. J. **42**:128 (Feb.) 1940.

An attack of rheumatic infection is not an isolated incident in a person's life but is one of a long and progressively damaging series of events extending from childhood through adolescence, to adult life.

There are two age periods when rheumatic heart disease is more common, first, that from 5 to 7 years and, second, that at 9 or 10 years, when the rise is more precipitous.

The commonest sign of rheumatic heart disease is a low-pitched systolic murmur at the apex, associated frequently with a clinically recognizable enlargement of the area of relative cardiac dulness.

Of 121 children admitted to the rheumatic service of Children's Memorial Hospital, Montreal, 10 had such murmurs, but heart disease never developed, while heart disease developed in 35 others of same group.

The average age at onset of cardiac disease was 8.83 years. The first clinical manifestations of rheumatism were: acute rheumatic fever, in 25 children; chorea, in 5; rheumatic heart disease, in 3, and acute tonsillitis, in 2.

Mitral insufficiency was noted in 12 patients; it was associated with stenosis in 11 others and with aortic disease in another 12. Enlargement of the heart, determined by roentgen examination, was present in 27 of the 35 patients.

Three observations which may be used in the determination of cessation of activity of rheumatism are (1) steadily rising weight curve; (2) a normal sleeping pulse rate; (3) normal rate of sedimentation. The latter indication is not specific.

MOORE, Omaha.

THE PREVENTION OF CONTACT INFECTION IN CHILDREN. NORMAN T. WELFORD, Illinois M. J. **78**:435 (Nov.) 1940.

Welford discusses the advisability of measures for the prevention of contact infections in children. A program toward that end was inaugurated at LaGrange during the past year.

BARBOUR, Peoria, Ill.

FUNGI AND FUNGOUS DISEASE. FREDERICK W. SHAW and J. D. REID, J. Lab. & Clin. Med. **26**:257 (Oct.) 1940.

The authors discuss the symptoms and laboratory methods of use in the diagnosis of several less commonly recognized mycotic infections, namely, chromoblastomycosis, torula meningitis and systemic histoplasmosis.

GARD, Galveston, Texas.

RHEUMATIC INFECTION IN CHILDREN IN THE DEEP SOUTH. JAMES EDWIN BAILEY, New Orleans M. & S. J. **93**:240 (Nov.) 1940.

The author is of the opinion that rheumatic infections are relatively infrequent in the deep South. The classic signs and symptoms are usually absent, and the sequelae are milder.

BERKLEY, Los Angeles.

A SIMPLE TREATMENT OF INFANTILE CHOLERA: ALKALINE WATER ORALLY AND RECTALLY AND DEXTROSE-SALT SOLUTION SUBCUTANEOUSLY. GÉRARD-LEFEBVRE, Bull. Soc. pédiat. de Paris **37**:316 (June) 1939.

The author summarizes "four cures of 4 desperate cases" of dehydration in infants resulting from diarrhea and vomiting. From 100 to 200 cc. of alkaline water was given orally six times daily, a similar quantity rectally two or three times daily and from 100 to 200 cc. of isotonic solution of dextrose and sodium chloride subcutaneously. Marked improvement occurred in twenty-four hours.

BENJAMIN, Montreal, Canada.

PRODUCTION OF AGGLUTINATING ANTIBODIES IN LEISHMANIASIS. G. MURANO and F. VECCHIO, Pediatria **47**:863 (Oct.) 1939.

The authors studied the effect of a typhoid-paratyphoid vaccine on the production of antibodies in 6 infants affected with leishmaniasis and in 3 normal infants. The vaccine was given intramuscularly every four days in increasing amounts. The titer of agglutinins for typhoid and for paratyphoid A and B in the serum was determined. The production of agglutinins was more marked in the infants affected with leishmaniasis than in the controls. The authors believe that the increased production of antibodies cannot be used to evaluate the defensive capacity of the organism in the presence of this disease. From their work they conclude that the antibodies are formed in the histioid cells of the reticulohistioid system.

MARTOCCIO, Utica, N. Y.

A CLINICAL PAPER ON ACUTE ARTHRITIS (ACUTE RHEUMATIC FEVER). EUGEN KRAMAR, Jahrb. f. Kinderh. **149**:108 (May) 1937.

The observations regarding the heart are most important. Frequently damage to the heart manifests itself in conjunction with symptoms in the joints. The symptoms in the joints may be slight. The greatest danger to the heart was found in the cases of younger children, especially those under 6. Nodules and the various types of erythema were often observed. The duration of the active process often extends to eight or ten months. Anemia was found to be a prominent feature, often severe enough to mask the primary cause of trouble. Hepatitis simplex was found occasionally. Prolonged rest under hygienic conditions is stressed as most important in treatment.

LANDAU, Hannibal, Mo.

DIAGNOSIS OF TYPHOID FEVER BY ASPIRATION OF BONE MARROW. KURT KÖRNIG, Kinderärztl. Praxis **11**:215 (July) 1940.

Körnig gives a brief description of the physical and laboratory data in the case of an 11 year old boy. A tentative diagnosis of typhoid fever had been made. Cultures of the stools, the urine and the blood, as well as serum agglutinations, however, gave negative results. A culture made in bile from specimens of bone marrow aspirated from the sternum gave a strongly positive result and established the diagnosis.

HEYMANN, Cleveland.

BACILLARY DYSENTERY. H. CURSCHMANN, Med. Klin. **35**:1473 (Nov. 17) 1939.

Curschmann discusses the bacteriology, epidemiology and symptomatology of dysentery in civil and in army life. Stool cultures and agglutination tests are important in diagnosis. Ordinary stool cultures yield a low percentage of positive results, but cultures of mucus obtained from the colon with a catheter are positive in a much higher percentage of cases. In the army protective inoculation is considered worth while. Therapeutically, polyvalent serum is recommended.

SIEMSEN, Chicago.

RAT-BITE FEVER IN KWEIYANG. C. S. YANG, Chinese M. J. **58**:245 (Aug.) 1940.

The disease has received little attention in China, but the city of Kweiyang is highly infested with rats, so that infants and children frequently are bitten. The author reports 2 cases in which the patients were nurses. Spirillum minus was obtained in both instances. Each patient was given one dose of neoarsphenamine (0.3 Gm.) and recovered.

NEFF, Kansas City.

FAMILIAL EOSINOPHILIA DUE TO ANCYLOSTOMA DUODENALIS. T. ITO, Acta pædiat. japon. **46**:763 (July) 1940.

The author reports his observations on the occurrence of pronounced eosinophilia due to Ancylostoma duodenalis in a family of six children. Both parents were infested with the parasite, and 5 of 6 siblings likewise showed evidence of infestation. The total leukocyte counts and the eosinophil percentages were as follows:

	Total Leukocyte Count, Per Cu. Mm.	Percentage of Eosinophils
Father	17,000	74.5
Mother	7,200	27.0
First child	11,200	33.0
Second child	20,200	68.0
Third child	22,000	71.0
Fourth child	15,000	61.5
Fifth child	10,600	47.0
Sixth child	9,000	1.5

Careful examinations of the stools revealed the presence of ancylostoma ova in every instance except in the nursling (the sixth sibling); no other demonstrable cause of eosinophilia could be found in any member of this family.

KATO, Chicago.

Chronic Infectious Diseases

ACUTE NECROSIS OF THE LIVER IN INFANTS FOLLOWING SODIUM BISMUTH THIOGLYCOLLATE ADMINISTRATION. IRVING J. WOLMAN, Am. J. Syph., Gonor. & Ven. Dis. **24**:330 (May) 1940.

The use of bismuth compounds intramuscularly in the treatment of syphilis is discussed, with particular reference to congenital syphilis; the author points out the danger, especially of the production of acute yellow atrophy of the liver. Two cases are recorded, 1 of a baby who did not have a diagnosis of congenital syphilis but had a presumptive diagnosis. Treatment with a bismuth compound was instituted, and the child followed a rapid down grade course and died. The autopsy showed acute yellow atrophy of the liver.

The second case was that of a child who had a doubtful serologic diagnosis of syphilis, although it looked like a positive one. This child was treated with the same drug but did not die until it was 9 months of age. Autopsy showed, again, acute yellow atrophy of the liver.

The author calls attention to the fact that the term for designating the condition should be "acute necrosis of the liver" rather than "acute yellow atrophy." He points out the rarity of the disease in infancy and cautions against the use of thio-bismol (sodium bismuth thioglycollate).

ROYSTER, University, Va.

THE TUBERCULIN PATCH TEST AND THE MANTOUX INTRADERMAL TEST. A. J. PEARSE, RALPH I. FRIED and VERA A. GLOVER, J. A. M. A. **114**:227 (Jan. 20) 1940.

The Mantoux test, with two strengths of old tuberculin, and the Vollmer patch test were made on 712 school children. Agreement between the two occurred in 87 per cent; 9 per cent of the patients gave positive reactions to the patch test only and 2 per cent positive reactions to the Mantoux test only.

The authors feel that the patch test is more suitable than the Mantoux test for testing children with tuberculin on a large scale.

HEERSMA, Kalamazoo, Mich.

EPITUBERCULOSIS. W. B. WOOD, Tubercle **20**:205, 1939.

Epituberculosis (Eliasberg and Neuland, 1920) is a manifestation of postprimary tuberculosis in childhood and occurs in a period characterized by enlargement of the bronchial glands and a tendency toward exudation. The chief factor in its production is atelectasis due to blocking of bronchi by tuberculous glands. A secondary factor is probably exudation into the alveoli and engorgement, the result of lymph stasis and vascular congestion. Tuberculous allergy possibly also plays a part, for allergic reactions are common in the second stage. If caseation of a gland leads to rupture of the wall of a bronchus, caseous bronchitis or bronchopneumonia may entirely alter the clinical picture and cause permanent damage to the lung. If the bronchial wall escapes such ulceration, restitution can occur and the collapsed lobe return to its original condition. A failure to reexpand must in either event give rise to bronchiectasis, which is not an uncommon result of tuberculous adenitis. One cause of the hilar flare phenomenon is atelectasis of the middle lobe of the right lung due to bronchial compression. Collapse of the apical division of the lower lobe may cause a similar shadow and have a comparable origin. Many of the triangular shadows based on the hilus are evidently due to local atelectasis, but care is needed in interpretation, for other lesions of a tuberculous and of a nontuberculous nature may cause similar opacities. The term "epituberculosis," which has served its purpose and drawn attention to the condition, might now be abandoned.

CORPER, Denver. [ARCH. PATH.]

TUBERCULOSIS OF THE BONES AND JOINTS; ASSOCIATION WITH PULMONARY TUBERCULOSIS. HELMUT FRANK, Beitr. z. klin. Chir. **168**:337, 1938.

In a study of 1,003 cases at Heuberg Sanatorium, the author made the following observations:

1. In infants and children, pulmonary tuberculosis commonly appeared at the same time as disease of the bones or joints. This was also a common finding in elderly people.

2. In persons between 10 and 20 years of age the coincidence of pulmonary tuberculosis and disease of the bones or joints was uncommon.

3. Operation was not contraindicated if pulmonary disease was present. As a matter of fact, successful operations influenced the condition of the lungs favorably.

RUBIN, Boston.

Diseases of Blood, Heart and Blood Vessels and Spleen

EFFECT OF SULPHANILAMIDE COMPOUNDS ON ENDOCARDITIS. RALPH H. MAJOR, Am. J. M. Sc. **199**:759 (June) 1940.

In a small series of patients with endocarditis lenta who were treated with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3,6′-disulfonate) and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) the author and his associates noted in some instances a fall of temperature to normal and disappearance of the organisms in the blood stream.

They thought it possible that in some cases, in which the vegetations were small, healing may follow. In other cases, in which the vegetations were more extensive, the organisms will probably live for a long time embedded at the base of the vegetations, although the blood stream remains sterile.

The rate of sedimentation of the blood has been found to be of great value in determining the activity of endocarditis. The rate of sedimentation has become normal in patients who apparently have recovered. In other patients, even though the temperature had fallen to normal and the blood stream remained sterile, the sedimentation rate was that of an acute infection. This made the author and his associates suspicious that the processes remained active, a suspicion confirmed by the subsequent course of events. In two such patients the cessation of treatment with sulfapyridine resulted in the reappearance of the organisms in the blood culture.

EMKE, Omaha.

SICKLE-CELL ANEMIA IN A WHITE FAMILY. LOUIS GREENWALD and JOHN B. BURRETT, Am. J. M. Sc. **199**:768 (June) 1940.

Five of 23 members of a white Italian family of Sicilian birth or extraction showed sickle formation of the red blood cells. The ancestors of this family were born in Naro, Sicily, and lived there. The parents of the persons whose cases are reported immigrated to the United States thirty-two years ago. The 5 subjects can be classified into two groups, those with anemia or sickle cell anemia and those without anemia or sicklemia. The entire group of 5 persons showed the sickle-forming phenomenon and constantly decreased fragility of the erythrocytes. It is emphasized that in obscure cases of hemolytic anemia in white patients, especially those from Mediterranean countries, wet preparations should be applied repeatedly, with careful technic. By this means sickle formation may be demonstrated. Because of the unusual opportunity presented in the study of this group, which demonstrates various phases of the disease from the active to the latent stages, the suggestion is advanced that those having the sickle cell trait represent patients with sickle cell anemia in one of its phases.

EMKE, Omaha.

SOME STUDIES IN THE MECHANISM OF CARDIAC HYPERTROPHY. GEORGE HERRMANN and GEORGE M. DECHERD JR., Ann. Int. Med. **13**:794 (Nov.) 1939.

After consideration of some theories of the mechanism of cardiac hypertrophy the authors report the results of their animal experimentation and conclude that injury resulting from temporary cardiac dilatation alone is not sufficient to produce cardiac hypertrophy.

READING, Galveston, Texas.

THE ERYTHROCYTE SEDIMENTATION TEST (OBSERVATIONS ON SEDIMENTATION RATES AND LEUKOCYTE CHANGES IN ONE HUNDRED AND THREE HOSPITAL CASES). ROBERT O. GREGG and ELLERY G. ALLEN, New York State J. Med. **39**:2192 (Dec. 1) 1939.

In a series of 103 hospital cases the sedimentation rate appeared to be a more reliable index of the degree of destruction of tissue than the total leukocyte count, the polymorphonuclear percentage or the nonfilament percentage. The increased nonfilament count seemed more indicative of damage to tissue than the polymorphonuclear percentage.

AIKMAN, Rochester, N. Y.

A CASE OF CONGENITAL COMPLETE HEART-BLOCK: THE EFFECT OF ATROPINE. GEORGE M. CURRIE, Brit. M. J. **1**:769 (May 11) 1940.

"A case is described of congenital complete heart-block in a child aged 2, associated with patent interventricular septum and the attacks of Stokes-Adams's syndrome.

"Electrocardiograms under normal conditions and after the injection of atropine are reproduced. The results of graphic investigation are given, and from these figures is discussed the possibility of the reduction of complete to partial block; the balance of opinion is against this possibility.

"The disproportionate action of atropine on the dissociated auricular and ventricular rates is noted, and also the much quicker return of the ventricular rate to its original figure."

ROYSTER, University, Va. [Author's Summary.]

FAMILIAL HEMORRHAGIC ANGIOMATOSIS AND ITS OCULAR COMPLICATIONS. J. FRANÇOIS, Arch. d'opht. **2**:425 (May) 1938.

François briefly describes familial hemorrhagic angiomatosis. The condition was first described by Rendu in 1896 and subsequently by Osler in 1901. The anomaly has appeared in several hundred members of about 50 families in Europe and in America. It has been found in only 4 families in Belgium, the patient whose case is reported in this article representing the fourth family. This patient was a woman aged 74, whose chief symptom was profuse bleeding from the eye. The author feels that the interest in this case centers on the difference in the type of the conjunctival lesions as compared with those of the skin and in the absence of ocular complications. A rather complete bibliography accompanies the article.

MARLOW, Syracuse, N. Y. [ARCH. OPHTH.]

CARDIAC MALFORMATION. L. BABONNEIX and J. HOREAU, Bull. Soc. pédiat. de Paris **37**:347 (June) 1939.

A girl 7 weeks old had attacks of asphyxia particularly associated with the taking of food. There were dyspnea, tachycardia and depression above and below the sternum with inspiration. The heart was enlarged, and there was a loud systolic murmur but no palpable thrill. Necropsy revealed a large interventricular septal defect and bronchopneumonia.

BENJAMIN, Montreal, Canada.

CONSTITUTIONAL HEMOLYTIC BLOOD DISEASE. M. ACUÑA, Arch. argent. de pediat. **12**:487 (Nov.) 1939.

Acuña considers three types of blood dyscrasia: von Jaksch-Cooley erythroblastic anemia, hemolytic icterus and sickle cell anemia.

He points out that it is not difficult to differentiate these three types when they are clearcut and the symptoms characteristic. He points out that there are intermediate types with which sometimes symptoms common to all are associated. The differentiation of these types and the classifications of cases are difficult.

He believes also that there exist types of racial anemia with erythroblastosis and diminished cell fragility without, however, any changes in bones or any microscopic changes in the iron content of the erythrocytes.

The author describes these three anemias as primitive, congenital anemias that are accompanied by splenohepatomegaly, erythroblastosis and hemolysis. All three are constitutional hemolytic hemopathies but differ in their initial symptoms and in their subsequent course.

SCHLUTZ, Chicago.

FAMILIAL LEUKEMIA. A. DECASTELLO, Med. Klin. **35**:1255 (Sept. 22) 1939.

All writers have failed to mention Weiss's report of 1927 on the familial occurrence of leukemia, probably because of the misleading title of the publication. Weiss observed 3 cases in one generation and 2 in the next. Decastello reports a sixth case in this family (the third in the second generation). He briefly reviews Weiss's report and concludes that, with the exception of a single instance, the diagnosis seems certain in all cases.

SIEMSEN, Chicago.

POLYCYTHAEMIA VERA. OTTO GOBELL, Ztschr. f. Kinderh. **61**:423 (Dec. 22) 1939.

Because of the rarity of the disease during infancy, the author reports the case of a 10 month old infant, who apparently had been afflicted since birth. Several members of the family presented a plethoric appearance and had high red blood cell counts. The infant's blood had a hemoglobin content of 85 per cent and a red cell count of 8,500,000. The heart was normal.

Significant observations were: sensitivity to sound and light, cyanosis, curved finger nails, bulging fontanel, high blood pressure (130 systolic and 100 diastolic) and high spinal fluid pressure (500 mm.). The high blood pressure is interpreted as compensatory for increased viscosity of the blood. The infant was subject to attacks of severe cyanosis, dyspnea and extreme restlessness (the latter presumably due to severe headache).

The author discusses various factors which may influence the number of red cells. The metabolism of oxygen is of great imporance. Disturbances of oxidation may lead to an increase in red blood cells or to a decrease (as in myxedema). Therapy should be directed at enhancing oxidation. Therapy involving destruction of red blood cells and bone marrow may be harmful. The author reports encouraging results from the use of an extract of adrenal cortex and nicotinic acid amide.

SIEMSEN, Chicago.

CHANGES IN THE SURFACE TENSION OF SERUM IN DISEASES OF CHILDREN. A. SAITO, Orient. J. Dis. Infants **26**:51 (July) 1939.

The surface tension of normal serum from children has a relatively constant value of 57.72 dyne/cm. By employing DuNoüy's tensiometer, the author found that during the first ten days of scarlet fever the surface tension of serum decreased by 2.50 dyne/cm., as compared with the normal standard, presumably because of the development of subicteric bilirubinemia. In infantile lead poisoning with marked bilirubinemia the surface tension of serum was remarkably diminished. In enteritis and intestinal intoxication, usually associated with considerable damage to the liver, the average decrease was 3.52 dyne/cm., whereas in acute dyspepsia with

good prognosis the surface tension values remained within the normal limits. In nephritis the decrease is due probably to chemical changes in the blood, such as increase in fibrinogen, nonprotein nitrogen and lipoids. In typhoid fever the decrease is due to the absorption of bacterial toxin and the impairment of the reticuloendothelial system, as well as to the formation of immune bodies.

KATO, Chicago.

EFFECT OF BODY MOVEMENTS ON THE PULSE RATE OF SICK CHILDREN. M. HAYAKAWA, Acta paediat. japon. **46**:146 (Feb.) 1940.

Hayakawa studied the effect of various movements of the body on the pulse rates of 167 sick children in Tokyo Imperial University Hospital. It was found that during sleep the average pulse rate decreased by 11 per cent; this was especially noticeable in children suffering from chronic endocarditis. An increase of 35 per cent was noted during crying. The influence of physical examination on the pulse rate was seen by the average increase of 17 per cent. When the convalescent children were made to take sitting-up exercise for one, two, five and ten minute periods, the average increase in the pulse rate ranged from 12 to 17 per cent. After the convalescent children were made to walk 50, 100, 200 and 500 steps on a level floor, the increase was from 10 to 15 per cent; the pulse returned to the normal rate within a short time, in proportion to the stage of the child's convalescence.

KATO, Chicago.

INFLUENCE OF VARIOUS DIETARY CONSTITUENTS ON MILK ANEMIA. K. SAKURAI, Acta paediat. japon. **45**:1487 (Nov.); 1629 (Dec.) 1938.

Sakurai endeavored to ascertain the effects of various nutrient elements on the blood and the blood-forming organs of young albino rats which were rendered anemic on an exclusive diet of milk. He reports the following observations: 1. Of all carbohydrates tested, galactose or lactose added to the basic ration produced the greatest effect in improving the anemic condition of these animals. Lactose, however, produced a pronounced decrease in body weight, while polished rice powder caused the greatest increase. 2. Casein exerted the most remarkable beneficial effect on the blood picture, while albumin arrested the further progress of anemia. 3. Of all the vitamins studied, B complex in the form of yeast had the most favorable influence against anemia, while vitamin C stopped the progress of anemia. 4. None of the fats or lipoids studied showed any effect on anemia. 5. Of the minerals, ferric chloride and copper sulfate, especially when the two were given together, showed the greatest effect. 6. Acid milk also produced a favorable result, probably because of improved utilization of iron in the milk. 7. Vegetable protein, in the form of powdered dried beans, exhibited a favorable effect on hemopoietic activity, owing largely to the presence of iron, copper, protein and vitamins in relatively large quantities.

KATO, Chicago.

Diseases of the Nose, Throat and Ear

SIGMATISM AND MALPOSITION OF THE TEETH. EUGEN SCHORR, Am. J. Orthodontics **25**:1143 (Dec.) 1939.

Man is born with two phenomena of coordination, breathing and sucking. For both, certain muscles are innervated, already coordinated. Apart from these two phenomena, coordination can be learned only through self experimentation. Normal coordination of the lips, tongue and mandibular muscles takes place when the infant sucks at the breast. A bottle-fed baby will learn a special but not natural kind of coordination. In sucking at the breast the infant lowers, thrusts forward and raises the mandible in a sequence. Thus the physiologic distal bite of the newborn infant is removed. Bottle feeding is entirely mechanical. The tongue is pressed

against the anterior portion of the maxilla and presses the milk out of the nipple. The author expresses the conjecture that the tendency, evident in cases of sigmatism, to thrust the tongue too far forward is probably due to the same impulse as that required in bottle feeding. LEWIS, Dayton. [ANGLE ORTHODONTIST]

X-RAY TREATMENT IN INFECTIONS OF TONSILS AND PHARYNX. G. GHOSH, J. Indian M. A. **9**:413 (June) 1940.

The benefits derived from roentgen treatment of infected tonsils are sufficiently definite to warrant its use. The types of patients most suitable are (1) patients with frequent colds but otherwise good health; (2) patients with heart disease in whom the tonsils have been removed but infected tissue remains, and (3) patients with abundant lymphoid tissue in the pharynx not amenable to surgical removal.

TENNEY, Madison, Wis.

THERAPEUTIC EFFECT OF TONSILLECTOMY ON RHEUMATISM. FRANK KOTYZA, Časop. lék. česk. **76**:1681 (Oct. 8) 1937.

This report is based on 2,458 tonsillectomies from the clinic of Precechte. Rheumatism was the indication in 1,140 cases, or 46 per cent. There were a history of familial rheumatism in 172 and a history of parental tuberculosis in 6 per cent of the cases. The prodromal diseases, in the order of frequency, were measles, scarlet fever and diphtheria. The sex incidence was: females, 58.3 per cent; males, 41.7 per cent. The majority of the patients had acute or repeated tonsillitis definitely before the operation. Rheumatic attacks antedated acute tonsillitis in 54 per cent, and most of the others had rheumatism during the attacks of tonsillitis. Postoperative articular involvement took place in 4.8 per cent and inflammation of the joints in 1.2 per cent. There was rarely definite improvement of acute articular symptoms, though the best results were obtained when the operation was performed within a year after the onset of articular symptoms. Of a control group of 100 cases, improvement was noted in 94. Active endocarditis was considered a contraindication to any operative procedure.

STULIK, Chicago.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

DIFFERENTIAL DIAGNOSIS OF CAUSE OF RECURRING ABDOMINAL PAIN IN INFANTS AND CHILDREN. R. R. FITZGERALD, Canad. M. A. J. **42**:332 (April) 1940.

In Canada, in 1929, appendicitis was twelfth on the list of causes of death; in 1936 it had risen to ninth place.

Differential diagnosis of abdominal pain is at times very difficult. If it can be shown that the order in which the events occurred during an attack were, first, pain, then vomiting, then tenderness, then fever, this sequence itself is the strongest support for a diagnosis of appendicitis.

Various conditions which must be differentiated from appendicitis are discussed. Among these are congenital anomalies, traumatic conditions, inflammations other than appendicitis and new growths.

MOORE, Omaha.

SEX HORMONE CHANGES ASSOCIATED WITH LIVER DISEASE. SAMUEL J. GLASS, HUGH A. EDMONDSON and SYDNEY N. SOLL, Endocrinology **27**:749 (Nov.) 1940.

Of 14 male patients hospitalized for chronic disease of the liver, gynecomastia was found in 8 and testicular atrophy in all.

Bioassays yielded no combined but high free estrogen values with low or negative androgen values in the urine.

The data indicate a failure of the cirrhotic liver to inactivate estrogens, and it is suggested that the free estrogens are etiologically related to the production of gynecomastia in cases of advanced cirrhosis of the liver. JACOBSEN, Buffalo.

GASTROINTESTINAL DISTURBANCES AMONG INFANTS AND CHILDREN. ROGER L. J. KENNEDY, Wisconsin M. J. **38**:727 (Sept.) 1939.

The significance of vomiting and diarrhea varies greatly according to the age of infants and children. In differential diagnosis in the cases of the very young consideration must be given to congenital anomalies involving the esophagus, obstruction of the pylorus and the duodenum, diaphragmatic hernia, congenital syphilis and cerebral injury. Vomiting in infants 2 to 8 weeks of age suggests chiefly pyloric stenosis and pylorospasm. Vomiting accompanied by fever is frequent in beginning acute infections and contagious diseases. It is a symptom in such a great variety of diseases that one needs to be constantly on the alert, else the occasional child with appendicitis will be missed. Conversely, careful examinations are needed to prevent unnecessary surgical procedure. Evidence of acute symptoms in other members of the family helps in these differentiations, but this circumstantial evidence must be carefully verified by physical and laboratory examinations.

In cases of recurrent vomiting, if there is any doubt concerning the cause, roentgenologic study is needed. Intracranial neoplasms are suggested when persistent vomiting occurs, even though there be no headache.

Causes of diarrhea in infants are most often improper feeding and parenteral infections, but bacillary and amebic dysentery and typhoid should be considered. Celiac disease, tuberculous peritonitis and ulcerative colitis are less frequent, but to be ruled out in the diagnosis of conditions found in older children.

JANNEY, Wauwatosa, Wis.

INFANTILE CIRRHOSIS OF LIVER. M. P. PRABHU, Indian J. Pediat. **7**:121 (July) 1940.

While relatively rare in most parts of the world, cirrhosis of the liver is common in India. This is a report of 100 cases observed in the past seven years. It occurs almost exclusively among Hindus and is more common in Brahmins than in non-Brahmins. There is a distinct familial tendency. In most cases the patients are under 2 years of age, but there is no difference in the two sexes so far as the incidence is concerned. It is more common among the upper classes, and diet does not seem to be a factor.

At autopsy the liver is shrunken and stained green but of normal shape. Microscopically the outstanding feature is the diffuse replacement fibrosis centered around partially or completely occluded sclerosed hepatic venules.

The diagnosis depends on: (1) a history of insidious onset with distention of the abdomen, anorexia and pale stools; (2) enlargement of the liver; (3) distended veins on the abdominal wall; (4) no improvement on previous changes in diet, and (5) exclusion of other causes of enlargement of the liver. Treatment consists of administration of zinc oxide, 1½ to 3 grains (0.09 to 0.18 Gm.) per day, and of 3 to 5 units of insulin per day, with a bland diet. TENNEY, Madison, Wis.

BACTERIUM ENTERITIDIS INFECTIONS IN INFANTS. K. J. GUTHRIE and G. L. MONTGOMERY, J. Path. & Bact. **49**:393, 1939.

This paper describes a series of cases of infection of infants with Bacterium enteritidis (Gaertner's bacillus) and a single case of septicemic infection with Bact. enteritidis var. dublin. The majority of the cases of Bact. enteritidis infection occurred as a small epidemic in the nursery of a maternity hospital. The source of this epidemic was untraced, but the organisms were most probably milk borne. More than half of the children died. All showed moderately severe purulent

catarrhal enteritis with septicemia; of those whose infection was fatal, meningitis was present in over one third and purulent cholecystitis in one seventh. Infection with Bact. enteritidis is uncommon in young children. The present series appears to be the largest on record, and the high mortality rate with the remarkable parenteral lesions illustrates the extraordinary invasive power which these organisms assume in susceptible subjects. Meningitis has been reported occasionally in children infected with Bact. enteritidis, but the triad of enteritis, meningitis and cholecystitis recorded here appears to be unique. [ARCH. PATH.]

A CASE OF GLYCOGEN DISEASE OR VON GIERKE'S DISEASE. LUDBROOK, New Zealand M. J. **39**:208 (Aug.) 1940.

The patient in the case reported was a child aged 5 years and 8 months. The outstanding features in the case were dwarfism; hepatic enlargement without jaundice, ascites or splenic enlargement; extremely low levels of fasting blood sugar without symptoms of hypoglycemia; an abnormal dextrose tolerance curve; inability of epinephrine to cause a rise in the concentration of blood sugar, and acetone constantly present in the morning urine. The article is illustrated.

WEIGAND, Indianapolis.

HEPATIC DISEASE IN CHILDREN. PIERRE WORINGER, Rev. franç. de pédiat. **15**:313, 1939.

Under the name of lipogenic dyshepatitis, the author, in a long but clearly written paper, describes a disturbance affecting the liver which is encountered frequently in children. Its principal features are an increase in the size of the liver, digestive disturbances such as nausea, vomiting and anorexia, pallor, headache and curability by a diet free from fat. The age of predilection is from 2 years to puberty.

The enlargement of the liver is definite and should not be confused with the normally palpable condition of the liver which may be observed in the infant and young child. Definite menus for the fat-free diet are suggested. There may be a gradual return to a moderate consumption of fat, although children who have exhibited this condition will probably never tolerate large amounts of fat. The condition seems to be of a hereditary nature. LESLIE, Evanston, Ill.

HEMORRHAGIC INFARCT AND PERFORATION OF THE STOMACH IN A CHILD FOLLOWING A BURN. P. MANFRINI and G. GERUNDINI, Pediatria **47**:910 (Oct.) 1939.

The authors report the case of a 4 year old child with a large hemorrhagic infarct of the stomach resulting in perforation. Four months previously the child had suffered a burn of the buttocks. At operation a section of the stomach was removed for histologic examination. The child died shortly after the operation. The authors review the relation between infarct, hemorrhagic erosions and ulcer of Curling as complications of burns. MARTOCCIO, Utica, N. Y.

LOSS OF APPETITE IN CHILDREN. JULIUS SURÁNYI, Ann. pædiat. **155**:345 (Sept.) 1940.

Loss of appetite is a symptom which depends sometimes on a single local, physical or psychic change and sometimes on a deep-lying congenital change in the body or the mind as a whole. Again, it may accompany some systemic disease. The problem to be solved by the pediatrician is made difficult through the circumstance that physical and psychic causes, some within the child and some environmental, conflicting with each other, produce the disease picture. It is a chief duty of the pediatrician to be able to be useful and necessary in this developing condition.

AUTHOR'S SUMMARY.

PYLORIC STENOSIS IN INFANCY. WERNER SCHMID, Beitr. z. klin. Chir. **168**:483, 1938.

This is a complete discussion of the current literature on pyloric stenosis as to etiology, diagnosis, treatment and follow-up care. RUBIN, Boston.

ULCERATIVE COLITIS IN CHILDREN. E. GLANZMANN and H. ASCH, Jahrb. f. Kinderh. **148**:233, 1937.

The authors contribute reports of 2 cases of ulcerative colitis, which is rare in childhood.

Symptomatically the course is identical with that of the disease in adults. There is often a familial tendency to diarrhea. The acute onset of the disease in children is frequently preceded by an infection of the upper respiratory tract.

The mortality is high; 4 of 14 children (including those whose cases were reviewed from the literature) succumbed.

The temperature may be but slightly elevated, or hectic, septic or remittent, as during relapse. Loss of weight is often extreme, anemia is characteristic and osteoporosis has been found in several instances. An erythema nodosum type of skin disorder has been reported, as have ulcers of the skin and mucous membranes.

The therapeutic measures include feeding of banana and raw apple pulp, orange juice and raw liver purée. Numerous solutions for irrigation have been tried.

After failure of medical treatment, appendicostomy or ileostomy has been used in some patients, with a measure of success. LANDAU, Hannibal, Mo.

INTUSSUSCEPTION IN CHILDREN. JOSEPH PODLAHA, Bratisl. lekár. listy **17**:500 (Oct.) 1937.

Invagination in infants under 12 months of age is likely to be acute or strangulated, while in children over 5 years of age the invagination is more likely to be subacute or chronic. The cardinal symptoms are acute, intermittent, colicky abdominal pains, nonodorous vomiting, bloody mucoid stools or bloody rectal washings and an elongated tumor mass under the edge of the liver or pointing toward the navel. The cause is believed to be incoordination and atony during spastic peristalsis. Only in early questionable cases should a gravity contrast enema be used as a therapeutic measure, as the danger of perforation increases greatly with time. STULIK, Chicago.

THE MUSCULAR DYSFUNCTION IN GLYCOGEN STORAGE DISEASE. C. FAN and THERESA T. WOO, Chinese M. J. **58**:88 (July) 1940.

The case of a Chinese girl aged 6½ years is reported. It was found that the daily urinary excretion of creatine as well as of total creatinine was somewhat high, but there was a definite diminution in the tolerance for ingested creatine. This intolerance for creatine may be explained by the lack of availability of muscle glycogen in the resynthesis of phosphocreatine. Disturbances in the muscular system are reported frequently in the literature; in the 49 cases mentioned by the authors many of the patients were infants.

Normally the energy metabolism of the skeletal muscles is dependent greatly on carbohydrates. In the table of approximately 50 cases collected by the authors all the patients were children, and 13 showed a muscular dysfunction, which was probably due to the fundamental metabolic defect in this disease.

NEFF, Kansas City, Mo.

A CASE OF GLYCOGEN DISEASE. N. SO and S. FUKUDA, Acta pædiat. japon. **46**:517 (May) 1940.

A case of a hepatonephromegalic type of glycogen disease in a boy 2 years and 4 months old is reported. Clinical and laboratory examination revealed

extreme enlargement of the liver, with moderate hypertrophy of the heart, fasting hypoglycemia, negative epinephrine hyperglycemia, marked sensitivity to insulin, a delayed blood sugar tolerance curve and acetonuria. Biopsy of the liver was attempted, and an excessive storage of glycogen was demonstrated. Treatment consisted in high voltage roentgen therapy over the liver, which seemed to induce temporary improvement, but the typical clinical picture recurred after the discharge of the patient from the hospital.

KATO, Chicago.

COMPARATIVE METABOLISM OF GLYCOGEN DISEASE, DIABETES MELLITUS AND RENAL GLYCOSURIA. K. SUZUKI and S. NONODA, Acta pædiat. japon. **46**:901 (Aug.) 1940.

The cases studied were: (1) a case of glycogen storage disease in a girl 2 years and 10 months old; (2) a case of diabetes mellitus in a girl 11 years and 11 months old, and (3) a case of renal glycosuria in a boy 5 years and 4 months old. In addition to the usual disturbance in carbohydrate metabolism, the coexisting anomalies of lipid metabolism in these cases were noteworthy. No lipemia was demonstrated in the case of renal glycosuria, but in the case of diabetes mellitus lipemia was marked. In the case of glycogen disease there was pronounced lecithinemia. Administration of insulin decreased the extent of lipemia in the case of diabetes, while the lipoidemia associated with glycogen dsease showed no change after insulin injection. Although no determinations were made, the authors suggest the possible relation of vitamin A to lipoidemia.

KATO, Chicago.

EXPERIMENTAL CHRONIC HEPATITIS (CIRRHOSIS) BASED ON INFECTION. T. T. ANDERSEN and S. TULINIUS, Acta med. Scandinav. **104**:550, 1940.

The author produced mild acute hepatitis in pigs by administering in the food either human duodenal juice from patients with epidemic hepatitis or minced liver from pigs with acute jaundice. Some animals were killed on the fourth day of this regimen, and mild acute hepatitis was found histologically (control animals had normal livers). The animals were given normal food thereafter and were kept in separate sties. They were killed after ten months, and, although the animals appeared normal, the livers of those experimentally treated showed increased lobulation, with much thickened septums, which invaded the lobuli. The arrangement of the cells was disorganized, with some degeneration; there were lymphocytic and plasma cell infiltration and adhesions on the moderately irregular surface. The liver was so hardened that the cut surface could not be depressed by a finger. The authors regard their results as evidence of the infectious origin of cirrhosis of the liver.

KAJDI, Baltimore.

STUDIES ON THE EFFECT OF INTRAPERITONEAL BLOOD TRANSFUSION. J. CLAUSEN, Acta pædiat. **27**:24, 1939.

Clausen has carried out experiments which demonstrate that several of the constituents of the blood are more or less efficiently absorbed into the circulation when deposited in the peritoneal cavity by abdominal puncture. An earlier paper described the rapid passage of antipneumococcus serum into the circulation. The present paper presents evidence obtained by agglutination methods that the donor's erythrocytes are also absorbed intact; the extent of such absorption was not determined quantitatively. The author's impression that the degree of absorption is sufficient to be clinically important is supported by the increase in the red blood cell count and in the hemoglobin concentration manifested by 4 infants who received intraperitoneal transfusions of whole blood.

MCCUNE, New York.

ROENTGENOLOGIC FOLLOW-UP EXAMINATION IN CONGENITAL PYLORIC STENOSIS AFTER THE MANIFEST STAGE. K. ANDRESEN, Acta pædiat. **27**:334, 1940.

Follow-up roentgen examination was carried out on 95 patients aged from 1 to 17 years who had previously been treated for pyloric stenosis. The subjects were members of the series reported on by Rinvik (*Acta pædiat.* **27**:296, 1940). Without regard to whether the treatment had been conservative or surgical, about half of the patients exhibited narrowing of the pyloric canal up to about 4 years of age; after that age constriction was encountered less frequently. The fact that the finding persisted up to the age of 17 years in some patients is taken to suggest that a connection may exist between congenital hypertrophic stenosis of the pylorus in infants and benign pyloric stenosis in adults. McCUNE, New York.

Nervous Diseases

FURTHER EXPERIENCE WITH THE USE OF SODIUM DIPHENYL HYDANTOINATE (DILANTIN SODIUM) IN THE TREATMENT OF CONVULSIVE DISORDERS. H. HOUSTON MERRITT and TRACY J. PUTNAM, Am. J. Psychiat. **96**:1023 (March) 1940.

Two hundred and sixty-seven cases of convulsive disorder were studied, in all of which the conditions were refractory to other forms of therapy. The ages of the patients varied from 2 to 68 years. The period of treatment varied from two to twenty-two months. The results were uniformly good, with seizures controlled for from two months to two years. JAHR, Omaha.

CONGENITAL DEMYELINATING ENCEPHALOPATHY. ROLAND P. MACKAY, Arch. Neurol. & Psychiat. **43**:111 (Jan.) 1940.

The author reports the results of pathologic study of 3 children having microcephalic idiocy, convulsions and cerebral spasticity, who died of intercurrent infections during the first three years of life. In all of the patients there was widespread demyelination and destruction of axis cylinders and glia without mesodermal infiltration. The author suggested that this type of condition should be designated as congenital demyelinating encephalopathy. BEVERLY, Chicago.

ADJUSTMENT OF THE ACID-BASE BALANCE OF PATIENTS WITH PETIT MAL EPILEPSY TO OVERVENTILATION. L. F. NIMS, E. L. GIBBS, W. G. LENNOX, F. A. GIBBS and DENIS WILLIAMS, Arch. Neurol. & Psychiat. **43**:262 (Feb.) 1940.

It has been pointed out that overventilation is particularly effective in precipitating seizures of petit mal. The purpose of this study was to determine whether this physicochemical state in patients with attacks of petit mal is different from that obtained in nonepileptic persons when they breathe or whether the nerve cells in the patients with attacks of petit mal are oversensitive to a change in the acid-base equilibrium.

The authors concluded: "The person with petit mal epilepsy responds to overventilation with a greater drop in the carbon dioxide content of the internal jugular blood and maintains the low level reached for a longer period after the overbreathing has ceased than does the nonepileptic control subject. The corresponding changes in the acid-base balance are such that the epileptic patient has an acid-base loop of greater area than the control subject. These findings can be explained on the assumption that the mechanisms which regulate the physicochemical state of the fluids of the brain are somewhat impaired in petit mal epilepsy, so that the person with such a condition is not able adequately to control or quickly adjust the acid-base balance when it is disturbed by overventilation."

BEVERLY, Chicago.

CONVULSIONS ASSOCIATED WITH TUMORS OF THE CEREBELLUM: CLINICAL AND PATHOPHYSIOLOGIC FEATURES. JOHN E. WEBSTER and LAURENCE M. WEINBERGER, Arch. Neurol. & Psychiat. **43**:1163 (June) 1940.

After a study of 158 verified cases of tumor of the cerebellum, the authors point out that convulsions not uncommonly occur in cases of cerebellar tumor.

BEVERLY, Chicago.

FOUR CASES OF PNEUMOCOCCIC MENINGITIS TREATED WITH SULFAPYRIDINE. F. H. MACKAY and E. F. HURTEAU, Canad. M. A. J. **42**:463 (May) 1940.

Sulfapyridine used in conjunction with the specific immune serum in the treatment of pneumococcic meningitis gave a more rapid and complete response than sulfapyridine alone.

Frequent determinations of the concentrations of the drug in the blood and cerebrospinal fluid are essential to indicate proper dosage.

The administration of the drug cannot safely be stopped in less than two weeks after the temperature and the cerebrospinal fluid cell count have become normal.

MOORE, Omaha.

A REGIONAL VOLUMETRIC STUDY OF THE GRAY AND WHITE MATTER OF THE HUMAN PRENATAL SPINAL CORD. A. M. LASSEK and G. L. RASMUSSEN, J. Comp. Neurol. **70**:137 (Feb.) 1939.

Lassek and Rasmussen studied the regional gray and white substance of the human spinal cord from a quantitative standpoint in a series of 19 Negro fetuses ranging in age from 3.9 to 10 lunar months. The length of the cord and the weight and gross volume were determined after removal of the pia. The cord was then impregnated with silver or with osmium tetroxide. The outlines of the gray and white substances were drawn, and the relative cross sectional areas were determined by measuring their outlines with a planimeter. Values were adjusted to correspond with the true volumes, determined earlier. From the ages of 3.9 to 10 lunar months, the total length of the spinal cord increased 2.8 times, the cervical portion 2.8 times, the thoracic 3 times, the lumbar 2.3 times and the sacral 2.2 times. At all stages the cervical portion averaged 26.2 per cent of the total volume of the spinal cord. The ratio of the length of the spinal cord to the body length gradually changed from 1:2.7 at the fetal age of 3.9 months to 1:3.3 at birth. The ratio of the volume of white substance to that of gray substance gradually increased from 0.8:1 at 3.9 months to 1:1 at 5.3 months and to 1.6:1 at birth. In the series studied, the white substance as a whole increased twice as fast as the gray, and the thoracic region exhibited the most striking changes in growth. At all stages of prenatal development the cervical region had the greatest amount of gray and white substance, followed in order by the thoracic, lumbar and sacral regions.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

STUDIES IN THE PHYSIOLOGY OF THE EMBRYONIC NERVOUS SYSTEM: II. EXPERIMENTAL EVIDENCE ON THE CONTROVERSY OVER THE REFLEX THEORY IN DEVELOPMENT. ZING YANG KUO, J. Comp. Neurol. **70**:437 (June) 1939.

Kuo offers evidence in the controversy over the reflex theory in development from experimental work on the embryonic nervous systems of the chick and frog. His experiments were devised to study various factors which determine whether a given response of the embryo in a given movement involves only one organ or more than one. Independent movements, spontaneous movements, in response to electrical stimuli were recorded. The responses of the forelimb, hindlimb, tail, eye and beak were observed. The development of somatic motility was divided into ten stages. The percentage of independent movements of each organ increased with age. The percentage of independent movements increased in quieter stages,

but dropped again when in the last stage, the stage of hatching, movements became vigorous and violent. Independent reflexes in response to electrical stimuli increased with age, but did not decrease at hatching. In later stages of development independent movements of the beak and eye were more numerous than those of other organs. Kuo found the following factors effective in movements: (1) stage of development; (2) environmental conditions; (3) health conditions of the embryo; (4) position of the embryo; (5) curarization; (6) intensity of stimuli; (7) interval between stimuli; (8) number of repetitions of stimuli; (9) strength and magnitude of the initial movements; (10) activity of body parts in different stages of development; (11) nature of movements previous to stimulation. Kuo says that his evidence does not lend support to either of the two current reflex theories.

ADDISON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

THE GOODENOUGH TEST (DRAWING OF A MAN) IN CHRONIC ENCEPHALITIS IN CHILDREN. LAURETTA BENDER, J. Nerv. & Ment. Dis. **91**:277 (March) 1940.

Six children with various types of encephalitis, all suffering from more or less definite neurologic deviations and serious personality defects, are reported on here. Outstanding features among them were overactivity, inability to inhibit impulses, destructiveness and limited span of attention. There was no definite general impairment of intellect, although there may have been some tendency toward a lower intelligence quotient so far as accomplishments in school were concerned. The neurologic deviations were related to oculomotor control, associated movements and extrapyramidal functions.

Though none of these children could be classified as mentally defective, all made a poor showing in the Goodenough test—out of proportion to their deficiency in other standard tests. "It represents," the author concludes, "an apperception of postural model, and probably arises from perceptual difficulties in relation to their own body rather than in optic perceptional difficulties."

JAHR, Omaha.

SUCCESSFUL CHEMOTHERAPY FOR HAEMOLYTIC STREPTOCOCCAL MENINGITIS AND PNEUMOCOCCAL MENINGITIS IN THE SAME PATIENT. W. OGILVY REID and JOHN F. LIBSCOMB, Brit. M. J. **1**:802 (May 18) 1940.

This is a detailed report on a patient with combined hemolytic streptococcus meningitis and pneumococcic meningitis who was successfully treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine).

ROYSTER, University, Va.

TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH SULPHAPYRIDINE. STEPHEN T. FELLA, Brit. M. J. **1**:804 (May 18) 1940.

Two patients with pneumococcic meningitis recovered after treatment with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Five patients treated with sulfapyridine before these 2 had died. It is thought by the author that an earlier diagnosis of the infecting organisms should be made if possible and that without any better knowledge of the dosage of sulfapyridine than is available at present, larger initial doses should be used in the pneumococcic and in the meningococcic form of meningitis.

ROYSTER, University, Va.

STUDIES OF WATER METABOLISM IN ESSENTIAL EPILEPSY. G. D. GREVILLE and TUDOR S. G. JONES, J. Ment. Sc. **85**:903 (Sept.) 1939.

Greville and Jones studied the diurnal water exchange in 2 epileptic patients for approximately four months and in a third patient for one month. Similar measurements were made on 2 nonepileptic patients as controls. No certain evidence was obtained that the urinary excretion was decreased before a fit and increased afterward, as has been often claimed. The water balance was determined daily as completely as was practicable. The daily excretion of chloride in the urine under constant salt intake at two levels also failed to show any

relation to the incidence of fits. Serial investigations were made of the concentration of constituents of the blood which might be affected by changes in the water content of the organism, viz., protein and nonprotein nitrogen in the plasma and hemoglobin and total solids in the whole blood. Here, again, contrary to the findings of other authors, the variations were apparently not associated with the incidence of fits.

KASANIN, San Francisco. [ARCH. NEUROL. & PSYCHIAT.]

POSTERIOR SEROUS MENINGITIS RESEMBLING TUMOR: SUBOCCIPITAL DRAINAGE (ODY'S OPERATION); CURE. PAUL GIRAUD, MICHEL SALMAN, PAILLAS and JEAN PROVANSAL, Bull. Soc. pédiat. de Paris **37**:359 (June) 1939.

A 12 year old boy had symptoms suggestive of cerebral tumor for a period of six months prior to his admission to the hospital. He had repeated generalized convulsions just before he was admitted. The spinal fluid showed increased pressure and a slightly increased content of protein. The nitrogen content of the blood was somewhat elevated. Suboccipital drainage was performed by a modified Ody technic (removal of the posterior arch of the atlas and incision of the dura). The patient gradually emerged from coma, which had persisted up to and during the operation, and regained complete motor power as well as vision. Postoperative hyperthermia was relieved by cold applications to the body. The patient was under treatment for congenital syphilis apparently because his mother had had a number of miscarriages. He had sustained an injury to the left side of the head two years previously. Lumbar puncture is considered inadequate and even dangerous in long-standing serous meningitis with markedly increased intracranial pressure.

BENJAMIN, Montreal, Canada.

PARAPNEUMONIC ENCEPHALITIS. F. DE FILIPPI and I. FERNANDEZ, Arch. argent. de pediat. **11**:22 (Jan.) 1939.

The authors report a case of parapneumonic encephalitis occurring in a child 3 years old. Eight days after the development of pneumonia, neurologic symptoms were present. These consisted of convulsions, spastic gait, loss of equilibrium and hyperexcitability. The spinal fluid was clear and showed normal signs. The symptoms seemed to be toxic in nature and not due to bacterial effects.

The case ended fatally, and autopsy showed petechial hemorrhage and paravascular infiltration, consisting mostly of mononucleocytes. There were degenerative foci in the cortex and central ganglions.

A review of the literature shows that in cases of postinfectious encephalitis there is a mortality of about 9 per cent. Sixteen per cent of the patients showed healing; 24 per cent showed some form of insanity, and 44 per cent showed psychoneurotic disturbances.

The severity of the infection does not bear any relation to the gravity of postencephalitic sequelae. Blood transfusions are recommended by the author as treatment.

SCHLUTZ, Chicago.

Psychology and Psychiatry

PSYCHIATRIC APPROACH TO THE TREATMENT OF EPILEPSY. STANLEY COBB, Am. J. Psychiat. **96**:1009 (March) 1940.

Forty-five persons with epilepsy, children and adults, were studied. The author admits that the problem is far too complex and the number of cases too small for satisfactory evaluation and analysis, but the indications are definite that a combination of medical therapy and psychiatric help yields better results than medical treatment alone. While sedatives are important, symptomatic aids to the physiologic functions of the epileptic patient (such as glandular therapy during the climacteric) constitute important additions to the care of the patient. "The epileptic, not the disease, must be the main concern of therapy."

JAHR, Omaha.

BEHAVIOR DEFICIENCIES IN MENTALLY RETARDED CHILDREN MEASURED BY A NEW BEHAVIOR RATING SCALE. A. A. STRAUSS and N. C. KEPHART, Am. J. Psychiat. **96**:1117 (March) 1940.

This study deals with high grade morons and children with a level of intelligence on the borderline of subnormal. Two types of impairment are recognized: (1) the exogenous, in which the deficiency is the result of cerebral trauma, such as birth injury or disease of the brain or its coverings, and (2) the endogenous, in which the deficiency appears as a familial or an individual property without apparent cause.

Eighty children were studied, 40 representing one type and 40 the other type of mental defect. The scale is divided into two parts: (1) motor behavior in general and bodily and facial movements during emotional states and (2) the personality in general.

Children with the exogenous type of deficiency are shown to be erratic, uncoordinated, uncontrolled, uninhibited and socially unacceptable. Those with the endogenous type present an appearance which is completely apart from the commonly accepted picture of behavior due to organic lesion or disease.

JAHR, Omaha.

DIRECT PSYCHOTHERAPY OF CHILDREN. MAXWELL GITELSON, Arch. Neurol. & Psychiat. **43**:1208 (June) 1940.

The author briefly describes the cause and treatment of behavior problems of children from a psychoanalytic point of view. The article is well written and the subject clearly presented. It especially points out to the pediatrician the need for recognition of emotional potentialities and careful guidance of emotional growth and development.

BEVERLY, Chicago.

THE STATUS OF THUMB-SUCKING AND FINGER-SUCKING. LELAND R. JOHNSON, J. Am. Dent. A. **26**:1245 (Aug.) 1939.

A résumé of the history of thumb sucking and finger sucking is presented. A comparison of the findings of 5 investigators is shown, and the results of a study of 989 orthodontic cases is presented (approximately one third from private practices and two thirds from an orthodontic clinic).

In 1930 Samuel Lewis stated: "There is a general tendency for malformations resulting from thumb-sucking to correct themselves if the habit is broken by the time the child is five years of age, but the malformations do not, as a rule, correct themselves if the habit persists." The author states: "In approximately one of every six cases of malocclusion, the habit of thumb-sucking or finger-sucking has been a contributing etiologic factor." In about 7 out of 10 children the thumb sucking or finger sucking habit is broken by 5 years of age, while 1 in 10 may continue the habit until he is over 10 years of age. Also about one quarter of the patients studied had broken the habit by 1 year or less.

Of 153 malocclusions due to thumb sucking, 50.98 per cent were class I, 47.7 per cent were class II and 1.3 per cent were class III. There are many different manners of thumb sucking.

In the deciduous dentition, if normal function of the lip does not exist or recur after the thumb or finger sucking habit is broken, the malocclusion (if any is present) will not correct itself; but if normal function of the lip does exist or recur, the malocclusion will tend to correct itself. "Prevention of the habit of thumb-sucking in infancy is advisable."

Mention is made of a palatal bar to break the suction of thumb sucking in order to eliminate the pleasure. Quotations from Freud and Levy on this subject are also presented.

STEADMAN, St. Paul. [ANGLE ORTHODONTIST]

THE DEVELOPMENT OF BEHAVIOR IN FOETAL SHEEP. JOSEPH BARCROFT and DONALD H. BARRON, J. Comp. Neurol. **70**:477 (June) 1939.

Barcroft and Barron have observed over 100 embryos and fetuses of sheep, ranging from 22 to 143 days of gestation. As early as the thirty-fifth day after insemination spontaneous movements were observed. The forelimbs, although poorly developed, moved, as well as the neck and trunk. Between the thirty-ninth and the forty-fifth day the neck of the fetus grew at such a rate that the head-neck length was roughly equal to the length of the trunk. During this period the spontaneous activity appeared to be initiated and controlled by the head and neck. By the forty-seventh day the eyes were seen to move as part of the general activity. Between the fifty-second and the sixty-fifth day the limbs became more independent of the trunk. Activity was induced by faradic current in both the head and the trunk. The greater part of the spontaneous activity of the fetuses of sheep appeared to be due to impulses reaching the central nervous system by primary afferent neurons. As development proceeded spontaneous movements became progressively less extensive.

FRASER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

BEHAVIOR PROBLEMS IN CHILDREN FROM HOMES OF FOLLOWERS OF FATHER DIVINE. LAURETTA BENDER, J. Nerv. & Ment. Dis. **91**:460 (April) 1940.

This paper deals with a group of children bewildered by the emotional instability of their homes, the insecurity and confusion being reflected in disorders of conduct. All these children are victims of the erraticism of their parents, whose credulity has robbed them of reason and whose fanaticism has replaced all semblance of social propriety.

JAHR, Omaha.

FEEDING IN INFANCY AND SUBSEQUENT PSYCHOLOGICAL DIFFICULTIES. B. C. F. ROGERSON and C. H. ROGERSON, J. Ment. Sc. **85**:1163 (Nov.) 1939.

The purpose of this investigation was to study the relation, if any, which exists between feeding difficulties experienced in infancy and the subsequent development of the child when he has attained school age, as measured by his achievement, behavior and psychologic status. The group of children studied did not belong to a psychiatric clinic, and it was hoped that the analysis of such a group would, in addition, throw light on the occurrence and relative frequency of psychologic difficulties in the period of childhood of a presumably normal section of the population. Children who were entirely breast fed during infancy were regarded as the group without feeding difficulties, and the children who received more or less artificial feeding in infancy, as the group with feeding difficulties. The term "infancy" has been used throughout to denote the period from birth to the introduction of solid foods into the diet.

The breast-fed group consisted of 62 and the artificially fed group of 47 children. The total number of children included in the study was 223, but only in 109 cases was it possible to have the intensive follow-up observation from infancy to the age of 7. The authors believe that the fact that a child had to be artificially fed is an indication of a feeding difficulty. In comparing the two groups they found that breast-fed infants showed marked superiority over artificially fed infants. Comparison of the two groups showed a higher percentage of sickly infants in the artificially fed group. The mothers of the children were carefully questioned as to the presence of various neurotic traits, such as sleep disturbances, enuresis, jealousy of younger children, fears, "nervousness" and terrifying dreams. The authors find a definite association between feeding difficulties in infancy and subsequent psychologic maladjustment of the child at home and at school.

KASANIN, San Francisco. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Genitourinary Tract

BILATERAL RENAL AND LEFT URETERAL CALCULI AND INFECTION OF THE URINARY TRACT IN A CHILD THREE YEARS OLD; OPERATIONS; MARKED IMPROVEMENT. P. LEREBOULLET, M. BOPPE, J. E. MARCEL and JEAN BERNARD, Bull. Soc. pédiat. de Paris **37**:301 (June) 1939.

A boy 3 years old had a colon bacillus infection of the urinary tract. Over a period of five months he was subjected to pyelotomy and ureterotomy on the left side and nephrotomy on the right side for the removal of multiple calculi. The child's general condition improved. It was the intention of the authors to examine him later to ascertain if the ureteral dilatation which was observed had disappeared and if any formation of calculus had recurred. BENJAMIN, Montreal, Canada.

CHRONIC NEPHRITIS: ARREST OF DEVELOPMENT IN AN INFANT OF THREE MONTHS; PROBABLE CONGENITAL SATURNINE ORIGIN. B. WEILL-HALLÉ and S. LOEWE-LYON, Bull. Soc. pédiat. de Paris **37**:312 (June) 1939.

A poorly nourished 3 month old girl showed evidence of nephritis with retention of nitrogen. The mother had taken considerable amounts of a preparation containing lead during pregnancy in an effort to abort. It was thought probable that this was responsible for the infant's renal disease.

BENJAMIN, Montreal, Canada.

URINALYSIS IN CHILDREN, WITH SPECIAL REFERENCE TO GLYCOSURIA. K. MIHARA, Acta paediat. japon. **46**:177 (Feb.) 1940.

The author examined samples of the urine of 1,648 children, with special reference to the occurrence of glycosuria. The observations were as follows: 1. The incidence of positive reactions to the Nylander and Benedict tests varied from 3 to 5.8 per cent in various groups studied. 2. The Benedict-Fujii reduction tests gave 0.077-0.212 per cent positive reactions. 3. Of the types of sugar found in all samples giving positive results, as determined by the osazone method, glucosazone was found in the greatest percentage (86); the remainder showed lactosazone, galactosazone and maltosazone. 4. The incidence of reactions positive for sugar was high in younger age groups. 5. There was no predilection as to sex. 6. A greater incidence was found during the summer months. 7. The p_H of the samples ranged between 5.4 and 6.2, and the average specific gravity was 1.020. 8. Albuminuria was encountered in 11.4 per cent. 9. Acetonuria almost paralleled the incidence of albuminuria. 10. No significant relations were seen between glycosuria and the dietary habits of children. 11. Tests for sugar tolerance performed on 4 children resulted in practically normal curves. 12. No constant relations existed between types of disease and glycosuria. 13. Follow-up urinalyses revealed that tests for glycosuria remained positive only in a limited number of the cases in which they originally were positive.

KATO, Chicago.

Diseases of the Ductless Glands; Endocrinology

THYROID GLAND DISTURBANCE AS A CAUSE OF UNEXPLAINED FEVER. ROBERT C. MOEHLIG, Endocrinology **26**:783 (May) 1940.

There is a certain group of patients who have a moderate rise in temperature (99 to 100 F.) for which no explanation or cause can be found. These patients are usually suspected of having pulmonary tuberculosis, undulant fever or a hidden focus of infection. As a rule, they have no symptoms. Those who have symptoms complain of fatigability, nervousness, irritability, insomnia, tenseness and a feeling of body tremor. To this may be added loss of weight of moderate degree, such as 5 to 10 pounds (2.3 to 4.5 Kg.). Frequently these patients have had

some infection before the onset of the fever. They are studied from all angles, including physical and laboratory examinations, without the establishment of a definite diagnosis.

The patients referred to by Moehlig have adenomatous goiter, and its removal results in the return of normal temperature. JACOBSEN, Buffalo.

BILATERAL LOCALIZED LESIONS IN THE HYPOTHALAMUS WITH COMPLETE DESTRUCTION OF THE NEUROHYPOPHYSIS IN THE PITUITARY DWARF WITH SEVERE PERMANENT DIABETES INSIPIDUS. A. B. BAKER and CHARLES B. CRAFT, Endocrinology **26**:801 (May) 1940.

Infantilism due to pituitary dysfunction is reported, occurring in an 18 year old girl who, at autopsy, showed bilateral localized lesions in the hypothalamus, limited almost entirely to the region of the supraocular nuclei. The patient manifested permanent severe diabetes insipidus.

A discussion is given of the relationship of the various lesions to the clinical findings. JACOBSEN, Buffalo.

ADRENAL CORTICAL VIRILISM. F. D. W. LUKENS and H. D. PALMER, Endocrinology **26**:941 (June) 1940.

At the age of 6 years, after an attack of scarlet fever, a girl began to develop a deep voice. At the age of 9 years she had a full beard, and her body was covered with hair. Operation at the age of 11 years revealed no abnormality of the adrenal glands.

At the age of 16 there was complete union of the epiphyses. At this time a second operation was performed, with removal of an adenoma of the adrenal cortex. The body hair and acne disappeared, the breasts developed and menstruation began. The urinary excretion of androgens was increased before the operation and became normal after it. Urinary excretion of estrogen was determined preoperatively by two methods, with widely different results; this may explain the findings of other authors in similar cases. A feminine psychologic pattern was observed throughout the period of masculinization. JACOBSEN, Buffalo.

TWO CASES OF HYPOPHYSIAL TUMOR IN CHILDREN, IN ONE OF WHICH IT WAS LATENT, MANIFESTED CLINICALLY ONLY BY A SPASMODIC LAUGH. GÉRARD-LEFEBVRE, Bull. Soc. pédiat. de Paris **37**:320 (June) 1939.

A boy 22 months old had the cardinal symptoms of tumor of the brain. Roentgenograms of the skull showed evidence of flattening of the sella turcica and destruction of the posterior clinoid processes. Treatment was apparently refused by the parents, and the child died later. Another boy, 12 years old, had a spasmodic laugh. He showed no other clinical evidence of tumor of the brain, but roentgenographic examination revealed increased intracranial pressure as well as abnormality of the sella turcica, which were interpreted as caused by a pituitary neoplasm. BENJAMIN, Montreal, Canada.

CUSHING'S SYNDROME OF THREE YEARS' DURATION IN A GIRL OF TWELVE YEARS: CLINICAL DETAILS—THERAPEUTIC DISCUSSION. GÉRARD-LEFEBVRE, Bull. Soc. pédiat. de Paris **37**:326 (June) 1939.

A girl had mumps at the age of 9 years. After this she began to grow abnormally big and fat, and pubic hair appeared, as in the normal adult female. She complained of severe and persistent headache. A complete examination of the eyes, including the fundi, gave negative results. Her blood pressure was markedly elevated. The urine showed some albumin but no sugar; the total output was about a liter daily. There was no abnormal mass in the abdomen. It is pointed out that it may be difficult to differentiate Cushing's syndrome from adrenal disturbance, and that the two conditions may coexist. In the absence of any evi-

dence of virilism or pseudohermaphrodism in this case, a diagnosis of Cushing's syndrome was made. Since there was no definite evidence of tumor, either of the hypophysis or the adrenals, radiotherapy to both of these regions was administered without definite improvement.

BENJAMIN, Montreal, Canada.

TRANSITORY FRÖHLICH'S SYNDROME ON A CONSTITUTIONAL BASIS. W. DZIERZYNSKI, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:81 (March) 1939.

Dzierzynski reports 5 cases of adiposogenital dystrophy in boys between 10 and 14 years of age. All showed definite improvement as they were observed for a few years. The syndrome was apparently benign and transitory. No roentgenographic or other evidence of organic disease of the perichiasmal or hypothalamic region was found. There was also no indication of chronic encephalitis. All the patients' mothers were obese and showed a tendency to hyperglycemia. All but 1 had hypercholesteremia. The author considers this syndrome a distinct clinical variant of Fröhlich's disease, probably with a constitutional genetic basis.

SAVITSKY, New York. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of Muscles, Bones, Joints and Lymph Glands

DENTAL OCCLUSION IN PATIENTS WITH MUSCULAR DYSTROPHY. JOHN C. BROWN and PAUL K. LOSCH, Am. J. Orthodontics **25**:1040 (Nov.) 1939.

Five cases of muscular dystrophy are reported, in 4 of which enlargement of the tongue is shown. In each patient there is beginning of actual arch deformity in the shape of open bite. The causative factors are believed to be a loss of muscular strength and an increase in the size of the tongue.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

BLUE SCLERAS COMBINED WITH ABNORMAL FRAGILITY OF THE BONES AND DEAFNESS (ADAIR-DIGHTON SYNDROME). H. ROSE, Arch. f. Ophth. **140**:278, 1939.

The syndrome of blue scleras, abnormal fragility of the bones and deafness should be named after Adair-Dighton (*Ophthalmoscope* **10**:188, 1912), the first person to describe it. Rose reports the pedigrees of 3 families, in each of which several members of different generations showed this syndrome. The mode of transmission was of the dominant type. The disease is discussed in the light of the new German laws, which aim at the elimination of hereditary diseases.

KRONFELD, Peiping, China. [ARCH. OPHTH.]

ACUTE OSTEOMYELITIS. W. INTHORN, Beitr. z. klin. Chir. **167**:251, 1938.

The author discusses the cases of severe acute osteomyelitis that were seen in the Marburg Clinic, in Marburg, Germany, between 1927 and 1936. The condition and the severity of the infection depend on the history of trauma and on the nutritional status of the patient, especially if the patient is a child. These cases are becoming less frequent than in the past. Inthorn reports that there were 83 cases, with 19 deaths in the period reviewed. In most of the cases the osteomyelitis was associated with generalized infection.

RUBIN, Boston.

FRACTURE OF THE NECK OF THE FEMUR IN CHILDREN. WALTER JEHN, Beitr. z. klin. Chir. **167**:447, 1938.

Fracture of the neck of the femur is an infrequent occurrence in childhood. The author reports the case of a 5 year old child who fell from a height and landed on the right leg. A roentgenogram revealed a fracture of the right neck of the femur. The right hip and leg were immobilized in plaster for two months. A perfect result was obtained.

RUBIN, Boston.

OLLIER'S DISEASE. WALTER STARK, Beitr. z. klin. Chir. **167**:513, 1938.

A complete description is given of the case of an 8 year old boy with a disease entity causing a disturbance of growth of various parts of the skeleton. The disease was first described by Ollier in 1899.

RUBIN, Boston.

ACUTE HAEMATOGENOUS OSTEOMYELITIS. R. HALL MCCOY and D. E. ROSS, Canad. M. A. J. **42**:162 (Feb.) 1940.

The cases are divided into three groups: In group 1 blood cultures were not positive on or shortly after admission of the patients to the hospital; in group 2 there was only a slight growth in blood cultures shortly after admission of the patients to the hospital; in group 3 there was a marked growth. In the first and second groups the organism found in the pus was Staphylococcus pyogenes; in 3 cases of the third group Streptococcus hemolyticus was found in the pus, and in the remainder, 8 cases, Staph. pyogenes.

Surgical drainage, best accomplished by the Orr method, is advised even in cases of severe septicemia accompanying acute hematogenous osteomyelitis.

The mortality rate in those cases in which the blood cultures showed Staph. pyogenes was 87 per cent; in cases with streptococcic septicemia, 33.5 per cent. Staphylococcic antitoxin appeared to be of no value in the treatment of patients with staphylococcic septicemia.

MOORE, Omaha.

LYMPHOGRANULOMA INGUINALE IN CHILDREN. C. E. SONCK, Acta dermat.-venereol. **20**:171 (March) 1939.

The author observed lymphogranuloma venereum in 5 girls whose parents suffered from the same disease. The girls belonged to three different families, and 3 of them were sisters. Most of the patients and their mothers presented involvement of the rectum, with stricture. Three girls also had hydrathroses of the knee joints. The disease in these small girls did not seem to show any essential differences in feature or course from that in adult women. The parents acquired the infection only after all the children were born; this excludes the possibility that the disease was inherited by the children.

These observations prove that lymphogranuloma venereum can be transmitted not only through sexual intercourse but also in other ways.

ASTRACHAN, New York. [ARCH. DERMAT. & SYPH.]

REGENERATION OF EPIPHYSIAL CENTERS OF OSSIFICATION. SAMUEL W. BANKS, WILLIAM KRIGSTEN and EDWARD L. COMPERE, J. A. M. A. **114**:23 (Jan. 6) 1940.

Five cases are presented, with findings obtained from roentgenologic examination, in which complete destruction of the epiphysial center and partial destruction of the epiphysial cartilage occurred in young children. In these 5 patients an ossification center developed later and progressed after the destruction by pyogenic or tuberculous infection. Evidence of the preservation of cartilage was seen on the roentgen films.

HEERSMA, Kalamazoo, Mich.

STILL'S DISEASE. J. CHAPTAL and A. SUQUET, Bull. Soc. pédiat. de Paris **37**:366 (June) 1939.

Chronic deforming arthritis, involving especially the distal joints of the extremities, gradually developed in an 11 year old girl. She presented, in addition, continued irregular fever, splenomegaly and adenopathy. The uric acid, calcium and cholesterol contents of the blood were normal. The white blood cell count was 16,000. The onset, two years previously, was acute, resembling polyarticular rheumatism. The child's general condition improved without any amelioration of

the joint manifestations. A sulfanilamide derivative was administered during the last several months of treatment. A higher percentage of cases of this rather rare condition was reported for the region where this girl lived than for other French districts where the disease had occurred.

BENJAMIN, Montreal, Canada.

Skin Diseases; Allergy

A CASE OF PROGRESSIVE SCLERODERMA WITH ASSOCIATED VITILIGO. E. DEGLOS and F. SAINT-GIRONS, Bull. Soc. pédiat. de Paris **37**:333 (June) 1939.

A girl 11½ years old had areas of pigmentation and scleroderma with intervening spots of vitiligo. The cholesterol content of the blood was slightly increased and the phosphatase high. Various organic extracts were administered, but these did not stay the development of new patches of scleroderma.

BENJAMIN, Montreal, Canada.

A CASE OF HEMORRHAGIC ANGIOMATOSIS. JULIEN HUBER, J. A. LIÈVRE and P. LAJOUANINE, Bull. Soc. pédiat. de Paris **37**:340 (June) 1939.

A girl 8½ years old had numerous pigmented and vascular tiny nevi on the face and a lesser number on the mucous membrane of the mouth. They appeared when she was 4 years old. She had hemorrhages from the nose, gums and stomach at times. Roentgenologic examination revealed a pedunculated tumor on the wall of the stomach. The blood was normal except for a slight increase in coagulation time. There was no family history of any similar condition.

BENJAMIN, Montreal, Canada.

BAZIN'S INDURATED ERYTHEMA: PROBABLE ENDOCRINE ORIGIN. B. WEILL-HALLÉ and A. ABAZA, Bull. Soc. pédiat. de Paris **37**:344 (June) 1939.

A girl 15½ years old had indurated erythema on the calves of the legs. The condition had been present for four months but cleared up after six weeks of administration of thyroid extract. A tuberculin test was negative. She had received BCG vaccine subcutaneously two years previously and had a weak positive tuberculin reaction about four months thereafter. Roentgenologic examination of the chest indicated nothing abnormal. A biopsy of the skin lesions was not obtained. The lesions are regarded as tuberculids by most dermatologists. No evidence of tuberculosis was established in this case.

BENJAMIN, Montreal, Canada.

Teeth and Dentistry

A CASE REPORT ON THE HEREDITARY FACTOR IN THREE CASES OF MESIOCLUSION. BROOKS BELL, Am. J. Orthodontics **25**:1079 (Nov.) 1939.

Three cases of class III are reported. In all a tendency for protrusive mandibles was noted in the mother of the subject and in 1 case of the maternal grandmother. Bell believes one should be conservative in prognoses of malocclusions of this type, for the limitation placed by inheritance surely controls the utmost extent of response to mechanical stimulation.

LEWIS, Dayton. [ANGLE ORTHODONTIST]

RATE AND DIRECTION OF ORTHODONTIC CHANGE AND THE EFFECT ON INCIDENCE OF CARIES IN FIVE HUNDRED ADOLESCENTS FOLLOWING CARIES, FILLING OR EXTRACTION OF FIRST PERMANENT MOLARS. J. A. SALZMAN, J. Am. Dent. A. **26**:1991 (Dec.) 1939.

A statistical study of caries with the various tables is presented. Loss of a first permanent molar results in "the inclination, rotation, elevation and bodily

movement of the remaining teeth" as well as deflection of the midline and asymmetry of the face. "There appears a rise in the incidence of caries in direct ratio to the number of first permanent molars extracted per child." Increase in the incidence of caries is "in direct ratio to the actual number of carious or filled first permanent molars when all of these teeth are retained in the mouth." The number of carious areas increases directly with the number of first permanent molars extracted as well as with the actual number of carious areas or fillings in the remaining molars. There is a higher incidence of caries in those mouths in which extraction of the first permanent molars has occurred than in those in which all are present.

Salzman draws the following conclusions: (1) The number of filled or carious first permanent molars can be used as an index to the incidence of caries in the mouth as a whole; (2) extraction of the first permanent molars is a direct factor in the increase in caries in the mouth as a whole, . . . (3) orthodontic and facial changes follow the disturbance of occlusion caused by extraction of first permanent molars. These results of extraction are the grounds for advocating the retention of the space of the first permanent molar as soon as it is extracted and for never sacrificing the first permanent molars as an orthodontic measure.

STEADMAN, St. Paul. [ANGLE ORTHODONTIST]

EXPERIMENTS DEALING WITH FACTORS INFLUENCING THE SHEDDING OF DECIDUOUS TEETH—PART I. RADIOGRAPHIC STUDY. H. H. SHAPIRO and W. M. ROGERS, J. Dent. Research **18**:73 (Feb.) 1939.

Since there are no experimental data regarding the accepted theory of resorption, experimental means were devised for testing the validity of the theory of pressure. Permanent tooth germs of the cat were removed at several stages of their development, before the onset of resorption of the deciduous root. The germ was removed on one side of the mandible only. The opposite side was used as a control. Observations are based on progressive radiographs. Cases in which there was operative root injury were eliminated.

The author concludes that when the developing germ of the permanent canine tooth in the cat is removed the deciduous tooth is shed but root resorption begins at a later time than on the control side, the side not operated on. There is some evidence of a slightly different mechanism of resorption when the pressure factor is eliminated. This is being studied histologically for a later report.

PREWITT, Lexington. [ANGLE ORTHODONTIST]

NEW IDEAS OF THE CALCIFICATION OF THE FIRST PERMANENT MOLAR. THIBAULT and JOSEPH, Rev. de stomatol. **41**:593 (Aug.) 1939.

The authors prosecuted their studies by means of histologic and roentgenographic and a combination of anatomic and roentgenographic methods. They conclude that the calcification of the first permanent molar does not generally start before birth. A detailed chart is given showing the time of appearance of the centers of calcification for both the mandibular and maxillary first permanent molars.

NEWCOMB, Cleveland. [ANGLE ORTHODONTIST]

Miscellaneous

THE ANTI-ENZYMATIC NATURE OF SULPHANILAMIDE'S BACTERIOSTATIC ACTION. RALPH R. MELLON, ARTHUR P. LOCKE and LAWRENCE E. SHINN, Am. J. M. Sc. **199**:749 (June) 1940.

Studies show that the free amino group of sulfanilamide when incompletely oxidized becomes poisonous for catalase and that, as a result, the toxic hydrogen peroxide produced by many pathogenic organisms is permitted to accumulate in the cultures.

In addition to catalase, other enzymes are adversely affected by the intermediate oxidation products of the sulfonamide compounds. As known so far, they are peroxydase, certain dehydrogenases and nitrotase. The nutrition of the bacteria is thus seriously affected, and bacteriostasis results.

The effect of such bacteriostasis against pneumococci in vivo is to bring about their "dissociation" into culture phases whose principal metabolic functions, including hydrogen peroxide formation and virulence, are so critically suppressed that the organisms fall easy prey to the destructive action of the phagocytes.

EMKE, Omaha.

THE USE OF 2-METHYL-1,4 NAPHTHOQUINONE (A SYNTHETIC VITAMIN K SUBSTITUTE). JONATHAN E. RHOADS and MAURICE T. FLIEGELMAN, J. A. M. A. **114**:400 (Feb. 3) 1940.

For 10 patients treated with this compound the increased prothrombin time was reduced in most instances. Hemorrhagic tendencies in 2 infants were benefited and the clotting time reduced, but in an infant with atresia of the bile ducts no benefit resulted.

HEERSMA, Kalamazoo, Mich.

MALIGNANT TUMORS IN CHILDREN. ELLIS KELLERT, New York State J. Med. **39**:2259 (Dec. 15) 1939.

Over an eleven year period, 15 of 2,050 malignant tumors of all kinds were found in children up to 15 years of age, a ratio of 1 tumor in children to 137 in adults. Only 1 of the 15 children is living, a 5 month old girl with a fibrosarcoma of the foot. At the time the article was written, two years had elapsed since she was first seen. All the others died in less than a year except a child with hypernephroma of the kidney, who lived two years. Excellent examples of the various types of malignant growth are reported. Kellert states that "no age is exempt from attack by any malignant neoplasm, and slight but persistent symptoms in children must be carefully investigated with the possibility of tumor kept in mind." In instances of unexplained pain, swellings or discolorations, tumor must be excluded. Biopsy is the most important diagnostic procedure. All such neoplasms should receive radiation, regardless of their histologic character.

AIKMAN, Rochester, N. Y.

METHODS OF RESEARCH FOR THE STUDY OF HEREDITY IN MAN. LEONE FRANZI, Pediatria **47**:573 (July) 1939.

The various methods of research for the study of hereditary pathologic conditions and the effect of environment and heredity on the individual person are discussed. Four methods of investigation of hereditary pathologic conditions are presented:

1. Analogous deductions from experimental results obtained from animals and from plants.
2. Deductions of correlation.
3. Genealogic method.
4. The study of twins.

MARTOCCIO, Utica, N. Y.

EXPERIMENTAL INVESTIGATION ON ETHYL CHLORIDE. LIEF EFSKIND, Beitr. z. klin. Chir. **167**:251, 1938.

The narcotic minimal concentration for ethyl chloride lies between 8 and 9 volumes per cent. The difference between the narcotizing and the lethal dose of ethyl chloride is similar to that with other inhalation anesthetics. In toxic doses ethyl chloride affects the respiration first.

The author's conclusion from his experimental studies is that with exact dosage and with enough oxygen ethyl chloride is apparently harmless.

RUBIN, Boston.

TOY DISHES AND ACUTE PLUMBISM. THOMAS K. RATHMELL and FREDERICK L. SMITH 2D, J. A. M. A. **114**:242 (Jan. 20) 1940.

The ingestion of a small amount of orange juice, cereal and fruit from new toy dishes produced severe vomiting, thirst and lassitude lasting less than a day. Examination revealed that the juice had absorbed lead from the toy dishes, supposedly of aluminum composition, and this was sufficient to produce acute plumbism.

HEERSMA, Kalamazoo, Mich.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

PHILIP ROSENBLUM, M.D., *President*

BENGT HAMILTON, M.D., *Secretary*

Regular Meeting, Feb. 18, 1941

Conservatism in the Treatment of Otitic Meningitis. DR. ROBERT B. LEWY and DR. ARCHIBALD L. HOYNE.

The increase of diagnostic ability and the additions to the therapeutic armamentarium have sharpened the judgment of the surgeon to such an extent that today one can expect a decrease in the number of unnecessary operations performed and a better outlook for both the patient who does and the patient who does not undergo an operation. The advent of sulfanilamide has focused attention on the problem of whether in cases of certain types of meningitis associated with the early stages of acute infections of the ear operation is necessary.

Meningitis could be defined as a condition in which the spinal fluid is cloudy and has an increased globulin content and cell count and on culture may or may not yield bacteria.

Unquestionably, sulfanilamide has improved the prognosis in cases of meningitis, although it may be erroneous to assume that the combination of sulfanilamide and mastoidectomy is necessary for recovery. Up to January of this year there had been recorded 13 cases of acute otitis media associated with meningitis in which recovery occurred with the use of sulfanilamide alone, and we have observed an additional number of unreported cases.

The cure of the patient with meningitis depends on many factors, including supportive treatment, proper nutrition, hydration and control of the acid-base balance. Mastoidectomy and removal of the mastoid process are not indicated when there is no necrosis of the mastoid process. Unless there is necrosis and unless by mastoidectomy and exposure of the dura of the middle and the posterior fossa the direct flow of infection is interrupted, there is no value in the operation.

The final decision as to treatment must necessarily rest with the otologist, since it is of the utmost importance to establish whether one is dealing with an early stage of an acute infection of the ear, to which therapy with sulfanilamide and its derivatives is applicable, or with an acute exacerbation of a chronic infection of the ear, in which case immediate surgical intervention may be imperative. The degree of necrosis of the mastoid bone must be evaluated; roentgenograms, physical examination and all other available means of securing information must be utilized, and the general condition of the patient must receive due consideration.

Illustrative charts and case histories were presented.

DISCUSSION

DR. ARCHIBALD L. HOYNE: I think one may say that the purpose of this paper is to emphasize the value of conservatism in the treatment of aural conditions, particularly those associated with scarlet fever. Every child with pain back of the ear or with meningeal signs attributable to mastoiditis does not require mastoidectomy. But it does not seem proper for the pediatrician to bear the entire responsibility for making the decision in regard to surgical intervention, and for this reason patients with conditions of the kind described should have the services of an otologist. Many children have been sent to contagious disease hospitals

during years past with requests for immediate surgical intervention, and yet many of these patients recovered without undergoing an operation.

It is interesting to recall that from 1930 to 1940, inclusive, 27,133 patients with scarlet fever were admitted to the Municipal Contagious Disease Hospital, and on 846, or about 3.1 per cent, mastoidectomy was performed. In some years the number of cases in which mastoiditis is associated with scarlet fever is much higher than in others. The season probably affects the incidence of scarlet fever and likewise the virulence of the causative organism. Few patients with mastoiditis die, and as a rule operations are performed late rather than early in the course of the disease.

DR. C. A. ALDRICH: I should like to ask Dr. Hoyne what percentage of patients with definite signs of mastoiditis, such as swelling and tenderness over the tip, had to be operated on and how much time elapsed before the operation was performed. I have records for a considerable number of patients seen in private practice, and about one fourth of those with definite signs were eventually operated on.

DR. M. P. BOROVSKY: I should like to ask whether repeated spinal puncture was part of the therapy in these cases.

DR. ARCHIBALD L. HOYNE: In reply to Dr. Aldrich, I cannot answer his question, but I do have some idea as to the number of patients with suppurative otitis media who require operation. Most of them, however, do not have meningeal signs. The decision to operate is left, so far as is possible, to the otologist.

In answer to Dr. Borovsky, spinal puncture was not performed for drainage. The idea that patients must be continually subjected to lumbar puncture to relieve intracranial pressure should be forgotten. I think that some persons believe that neurologists do not wish to give up the custom, but we have found that the spinal fluid clears up more rapidly and the patient recovers more quickly when numerous lumbar punctures are not performed. In some of the cases the spinal fluid showed high cell counts but no organisms. Even when organisms are present, if treatment is given with the drugs now available many patients recover without complications; often they are well at the end of a week. This is also true of both meningococcic and influenzal meningitis. A number of our patients with meningitis who recovered were subjected to only one intrathecal puncture, and that was performed solely for the purpose of diagnosis.

DR. ROBERT B. LEWY: My answer to the question about the percentage of patients with signs of mastoiditis who were operated on is brief. I do not know. Nobody does know, because there are two types of signs of mastoiditis, the subtle and the obvious. In a case with the obvious variety operation is indicated. When the subtle variety is present, at least one otologist of three would not agree that operation is indicated. I have operated in some cases in which the classic signs were absent and have not operated in some in which such signs were present, and I have not been sorry. I know that the point of view toward operations on the mastoid held in the East, particularly at Johns Hopkins University School of Medicine, differs from that held here. Physicians here are a great deal more conservative and wait for a longer period after the onset of symptoms before operating.

Apparently, a concentration of sulfathiazole (2-[paraaminobenzenesulfonamido] thiazole) in the spinal fluid adequate to cure meningitis cannot be attained. Some physicians think the drug is effective, some do not; I cannot give an opinion on that question.

A Study of Seventy Families in Which Cases of Rheumatic Fever Appeared. DR. ARTHUR ROSENBLUM and MRS. RUTH L. ROSENBLUM.

The familial occurrence of rheumatic fever has long been recognized. Reports of the incidence of the disease among other members of families in which there were children with rheumatic fever have varied considerably, but all agree that

there is an increased incidence in such families. The specific initiating factor, however, is a controversial matter. While rheumatic fever is a disease of the lower economic classes—not the very poor but the between-class poor families—it is not rare in the well-to-do classes. In most studies infection of the upper respiratory tract was the only factor which could be associated with the incidence of the disease, and one investigator came to the conclusion that the rheumatic state is a special type of response to chemical substances elaborated during such infections, the hemolytic streptococcus probably being the responsible agent.

The material for this study consists of 70 families in each of which there was a child with rheumatic fever who attended the Christopher Public School. Since December 1938 careful investigations have been made with regard to the environment, the family history, the social history and the nutritional background. Statistics were included only for those children whose disease was unquestionably rheumatic fever. The results are summarized in a series of twelve tables. A comprehensive review of the literature is given, and the conclusion is reached that the observations, like those made in other localities, showed the marked familial trend in the incidence of rheumatic fever.

Summary of the data shows that in families in which the parents had rheumatic fever there was a higher incidence of the disease among the siblings than among the children of parents who did not have the disease, that the rate of attack was higher among those who were in contact with a person with active rheumatic fever and that simultaneous attacks of the disease among siblings and among parents and children were frequent.

Infections of the upper respiratory tract preceded onset of the first manifestations of rheumatic fever in slightly less than one half of the cases. Scarlet fever preceded the onset in 10 per cent of the cases. In those cases in which there was no preceding infection of the respiratory tract a variety of factors was present, including exposure to dampness, chilling, tonsillitis and psychic trauma. There was no preceding illness in a number of cases.

Tonsillectomy did not seem to influence the recurrence of the disease. The older the child at the time of tonsillectomy, the fewer the recurrences. Generally, in the cases in which there was severe cardiac damage tonsillectomy either had not been performed or had been done after the onset of rheumatic fever.

There was a higher incidence in the self-supporting group than in the group on relief. The self-supporting group was on a marginal level, however. No relation between diet and the occurrence of rheumatic fever could be found. It was emphasized that most families studied did not have an optimum diet. The only environmental factor that could be correlated with increased incidence was dampness. There was no correlation of incidence and the presence of vermin.

An Epidemiologic Study of Rheumatic Fever Among Children in the Chicago Area: A Critical Survey of One Hundred and Ten Cases. DR. ETHEL M. DAVIS.

This study was undertaken to determine the various epidemiologic factors associated with rheumatic fever and to study the manifestations and course of the disease in childhood, with special consideration of prognosis. The major clinical manifestations of polyarthritis, chorea and rheumatic carditis are well known, and the so-called nonclassic manifestations in children are now being better understood.

The 110 children studied were seen in the children's cardiac clinic of Michael Reese Hospital and in the wards of Sarah Morris Hospital. They were admitted from the hospital after attacks of active rheumatic carditis, frank rheumatic fever and chorea and from the pediatric clinic because of rheumatic heart disease.

An intensive social service study of the families of 50 of the children under observation was undertaken to determine if factors pertinent to the disease could be brought to light. The various observations were tabulated and analyzed, with a view to corroborating clinical impressions about the factors influencing prognosis.

It was noteworthy that 33 of the patients with definite heart disease had never been hospitalized. Inasmuch as early recognition of the syndrome of rheumatic fever may prevent the development and progression of cardiac involvement, it is possible that earlier and more thorough medical care of these patients might have minimized cardiac damage. Apparently, there is a tendency for the existing lesions of rheumatic fever to heal. All but 3 of the 110 children are alive, and only 2 have suffered sufficient cardiac damage to make them invalids. It is only when the heart muscle is irreparably damaged early in the course of the disease or when reinfection continues to occur that the prognosis becomes serious.

In spite of the fact that both the cause and the means of cure of rheumatic fever are unknown, advance has been made in its management. Children with rheumatic fever are receiving better care now than they did twenty years ago, through early recognition of the disease, prompt hospitalization, adequate convalescent care and persistent medical supervision.

DISCUSSION ON PAPERS BY DR. AND MRS. ROSENBLUM AND DR. DAVIS

DR. STANLEY GIBSON: The paper by Dr. and Mrs. Rosenblum is a valuable contribution to the existing knowledge of rheumatic fever. It emphasizes the importance of a careful survey of the entire family, rather than a casual questioning of the parent, in an effort to determine the importance of the familial factor in the incidence of the disease. I was pleased to hear the statement that "growing pains" were infrequent among children with rheumatic fever. It has been my impression that they occupy a minor place and are not in themselves evidence of the presence of the disease. The importance of infections of the respiratory tract should be more fully appreciated. Unless the history is taken carefully, they are apt to be overlooked, especially when, as often happens, they occur three or four weeks before the onset of manifestations of rheumatic fever.

Dr. Davis emphasized the importance of chorea as a member of the series of rheumatic diseases. My associates and I have not found so high an incidence of cardiac involvement in cases of chorea as Dr. Davis has reported, but it is high enough to be significant. We have summarized the data in 1,487 cases of rheumatic fever and chorea. In 38 per cent of the 581 cases of chorea the heart was involved. I was amazed at the low mortality in Dr. Davis' series. We know that in 146 cases of our series death has already occurred, a mortality to date of about 10 per cent. Moreover, in 44 cases the first attack of rheumatic fever terminated fatally. Hence rheumatic fever must be regarded as a rather serious disease.

DR. LOUIS KATZ: These two interesting presentations show how definite knowledge can be obtained by ordinary careful clinical observations, without recourse to special apparatus, provided the studies are based on objective analysis and not on impressions. Furthermore, these studies show that while knowledge of the causative infectious agent would be important in more precisely defining the concept of rheumatic fever, considerable knowledge concerning its natural history could be obtained without knowledge of what organism produces it. However, precise knowledge of the infecting organism or virus would be of value in eliminating those conditions with a superficial resemblance to rheumatic fever which might be included in series of cases for study. Selection of cases could then be based on the etiologic factor and not, as now, on the clinical picture, and in this way some controversies would be eliminated. It does not follow that knowledge of the specific infectious agent will of necessity improve the management of the condition. The cause of bacterial endocarditis is known, but this information has not led to a cure of the disease.

It is important to emphasize that studies like these, which are based on personal observation, are of greater value than those based on a survey of hospital records, a method followed too often in the past.

The studies of Dr. and Mrs. Rosenblum seem to exclude diet as an important causative factor. Furthermore, their demonstration of a tendency to familial

occurrence should make the pediatrician who has a patient with active rheumatic fever examine the other members of the family for the disease.

Dr. Davis' experience with this small group is similar to that of Schlesinger, who found in working with a larger series that normal activity and normal social adjustment occur frequently and that a fatal outcome is not as common as has hitherto been believed. The point Dr. Davis stresses, that chorea should be considered a sign of potential rheumatic fever and not dismissed too casually, is worthy of further emphasis. Her point that early recognition and good medical management will lessen the detrimental effects of the disease is also of practical importance.

There is need of more studies such as these, and it is worth while that not only pediatricians but physicians dealing with adults who have rheumatic fever be made cognizant of the facts which these studies have brought forth.

DR. ARCHIBALD L. HOYNE: For many years scarlet fever has been looked on as one of the foundation stones for the development of rheumatic fever. I should like to ask Dr. Rosenblum and Dr. Davis how important a place they believe scarlet fever actually holds in the causation of rheumatic fever, not what the percentage of cases in which it is involved is according to history. I think if the history in regard to measles were obtained in every case of rheumatic fever it would be found that measles had occurred in a high percentage of them. Does the percentage really mean anything?

DR. BENGT HAMILTON: I have gained the impression that in some cases the rheumatic fever has had definite characteristics, such as the development of erythema annulare rheumaticum and nodules. I wonder if Dr. Davis has seen such characteristics in the cases of several members of the same family.

DR. P. RAVENNA: I was greatly interested in these papers because I think that epidemiologic studies are of the utmost importance for the proper interpretation of a disease, especially when the causative agent is still unknown. Although I have approached the problem of rheumatic fever from a bacteriologic point of view, I am continuously looking to clinical studies and especially to epidemiologic observations for inspiration and advice in outlining my research.

Scarlet fever preceded the onset of rheumatic fever in about 10 per cent of Dr. Rosenblum's cases. This incidence is in accord with the data reported by Shapiro in this country, by Moltschanow in Russia and by others in France. In cases of scarlet fever, however, joint pains occur which are not due to rheumatic fever. They are indications either of the so-called scarlatinal pseudorheumatism, which occurs in the first week of the disease, or of hemolytic streptococcic rheumatism, that is, true purulent polyarthritis, occurring about the third week. The true postscarlatinal rheumatic fever appears three to seven weeks after onset of the rash, and it occurs, as Dr. Rosenblum said, in about 10 per cent of the cases.

The relation between scarlet fever and rheumatic fever seems to be much closer. In 1914 Schmorl described Aschoff's nodules in the heart in a case of scarlet fever; this observation was readily forgotten, but others followed (Fahr, Siegmund) which proved that Aschoff's nodules are present with surprising frequency in cases of rheumatic fever. This observation involved the specificity of Aschoff's nodules, and therefore Aschoff discussed it and expressed rather discordant opinions in different articles published during the last few years. The question is still open, but it must be kept in mind not only in every discussion on the specificity of Aschoff's nodules but in all epidemiologic studies on rheumatic fever.

In an epidemiologic study it is extremely important to differentiate between the simultaneous occurrence of many cases and the occurrence of a small number of cases at one time followed by the occurrence of other cases after one, two or more weeks. The first type of epidemic of rheumatic fever is probably related to weather conditions, while the second is more frequently associated with, and indicative of, a true contagion.

I had occasion to observe several epidemics of the first type among soldiers. In Italy recruits were inducted in March, and nearly every year many of them fell sick almost simultaneously in April or May. This may be attributed to the exposure of nontrained persons to cold. Other epidemics have been described, however, in which the disease seemed to spread from one group to another and in which new cases occurred in small outbreaks regardless of the weather conditions. Two interesting epidemics of this type were described by two French authors, Grenet and Andrieu. Obviously, this type of epidemic suggests that contagion is the determining factor.

In order to investigate the importance of contagion, it would be interesting to compare the familial incidence of rheumatic fever, with consideration not only of the number of members of the family but of the number of people who live and sleep in the same room or in the same bed. Since a prolonged contact is probably necessary for the contagion of rheumatic fever, as it is for the contagion of tuberculosis, this type of investigation may show the danger of overcrowding. Incidentally, it is significant that no epidemics have been reported in schools, where children assemble for a few hours only, but many epidemics have been reported in institutions, where children live and sleep crowded together.

A last point on epidemiology should be noted. It has been my experience that rheumatic heart disease and polyarthritis are frequent in northern Italy. In southern Italy rheumatic heart disease is frequent but polyarthritis is rare. Similar observations were made in this country. Under such conditions, the diagnosis of rheumatic fever is made more easily in the North than in the South, and for this reason statistics on the occurrence of rheumatic fever at different latitudes may not be perfectly comparable.

DR. ARTHUR ROSENBLUM: In cases in which several members of the family contracted rheumatic fever the attacks did not occur on the same day but several weeks or months apart. With regard to home conditions, most of the families were large and were crowded into small quarters, so that usually several members slept in one bed.

DR. ETHEL M. DAVIS: Dr. Hoyne asked about the relation of scarlet fever to rheumatic fever. The study carried out by Paul gave conclusive evidence that scarlet fever may initiate or reactivate rheumatic fever in a susceptible person or in one from a family in which cases of rheumatic fever have occurred. The history frequently shows that manifestations of rheumatic fever appeared after scarlet fever.

The literature leads one to believe that nodules occur more frequently in cases of rheumatic fever in England than in this country. Here they are thought to be of serious prognostic significance. With reference to tonsillectomy, almost all children with manifestations of rheumatic fever who have not undergone the operation usually do so during a period of inactivity.

Book Reviews

L. Emmett Holt, Pioneer of a Children's Century. By R. L. Duffus and L. Emmett Holt Jr., M.D., with a foreword by Edwards A. Park, M.D. Price, $3. Pp. 295, with 19 illustrations. New York: D. Appleton-Century Company, Inc., 1940.

The life story of L. Emmett Holt will be eagerly read by a large number of physicians and pediatricians and also by those who are interested in the development and progress of child welfare. Holt was outstanding. He was not only a leader but an inspiration to his colleagues, as well as to social service workers, nurses and myriads of mothers who reared their babies according to the directions given in his book "The Care and Feeding of Children."

Holt was born March 4, 1855 in Webster, N. Y., a few miles from Rochester. Both of his parents were of New England origin. In his early youth Holt worked on the farm; he fed the stock, milked three cows and cleaned out the stalls before breakfast and did the same chores in the evening. Holt's mother, Sabrah Curtice Holt, is described as a woman of deep convictions and considerable force. She had a vivid, almost uncanny insight into human motives. She strove to teach her children self confidence and perseverance. She counseled economy and the respect and esteem of friends, and Holt, deeply impressed by his mother's precepts, followed these injunctions throughout his life. Many another illustrious man has acknowledged that his success in life was due to his mother's influence. Holt never tolerated failure, either in himself or in others; he never went into debt or allowed an organization with which he was connected to live beyond its means.

Holt received his early education in the little red schoolhouse. Then he attended the Webster Academy for four years. In 1871 he matriculated at Rochester University, where he received a so-called classical education, after the manner of the day; he studied Latin and Greek, modern languages, history, logic, rhetoric and mathematics. After graduation he taught for a year in the Riverside Academy, Wellsville, N. Y. At the end of the year he determined to go into medicine as a career.

He entered the Buffalo Medical College in 1876. It was a good school for its day, a proprietary institution of the conventional type. There were no laboratories. Anatomy was learned from textbooks, and physiology and pathology were left for the most part for the students to master for themselves. The microscope was neither used nor mentioned. The teaching consisted of a four months' lecture course on clinical subjects, and these lectures were repeated year after year.

After attending one course of lectures at Buffalo Holt, following the so-called preceptor system, which was common in those days, entered the office of Dr. Whitbeck, of Rochester, where he remained for eight months and read medicine.

He now began to wish for wider opportunities for advancement, and he determined to leave Rochester for New York. He was fortunate in securing a position at the Hospital for the Ruptured and Crippled in 1878, and shortly afterward he matriculated at the College of Physicians and Surgeons. At the Hospital for the Ruptured and Crippled, Holt came under the supervision of Dr. Virgil P. Gibney, a distinguished orthopedic surgeon. Holt felt he owed a deep debt of gratitude to Gibney, and they remained friends throughout their lives.

After his graduation from the College of Physicians and Surgeons in New York, Holt secured a position at Bellevue Hospital in the surgical service. He was particularly interested in pathologic studies, and it was his good fortune to become associated with Francis Delafield, the pathologist, and with William H. Welch, who had just opened a bacteriologic laboratory at Bellevue.

After finishing his service at Bellevue, Holt went into private practice. Patients came slowly at first, and to confine himself to a specialty was out of the

question at this time. He carried on a general practice, with some work in obstetrics, minor surgery and otolaryngology; indeed, he was willing to treat patients of all types. To relieve the monotony of waiting in the office for patients, and perhaps to offset the drains on the treasury, Holt started a quiz class in anatomy, which was successful.

At about this time Holt began to think of specializing in the medical disorders of children. He obtained a staff appointment to the Northwestern Dispensary, New York, and later he secured a position at the New York Infant Asylum at Mount Vernon, at that time an hour's ride by train from the city. Holt saw the opportunities for clinical investigation and study at this institution and took advantage of them. He early formed the habit of recording, tabulating and analyzing his clinical and pathologic observations, which later became the basis of his scientific papers.

Holt was appointed professor of pediatrics at the New York Polyclinic in 1891, a post which he held until 1901, when he became Jacobi's successor at Columbia University.

Edwards A. Park wrote the foreword for this book. He was a student and intern of Dr. Holt, whom he describes as a small, slender man, immaculately dressed. Of his lectures Park says: "He spoke in short, crisp sentences in a voice low and clear." Park characterizes Holt's clinics at the Babies Hospital as the best he ever attended. They were informal; every student was assigned a patient and was required to present the case with a brief history, a diagnosis if possible and an outline of treatment. The students appraised him as a masterful teacher.

Dr. Holt established the Babies Hospital in 1889. Such a hospital cannot be organized and maintained without infinite worries and cares. The man in charge encounters financial problems. He has to consider the details of hospital construction. Provisions for adequate nursing, medical care and administration require time and labor. All of these Dr. Holt surmounted. Eventually, in 1901, a modern seven story building was erected, with dispensary and laboratory facilities. This was the model infants' hospital of the period in this country. Investigative work was carried on, and pathologic studies were carefully conducted. The hospital was in every sense an institution of learning. Physicians and nurses came from home and abroad to listen to the master clinician, to visit in his wards and to receive instruction and inspiration. Dr. Holt continued at the helm of the Babies Hospital until 1923, and on it he lavished a devoted and parental care.

Holt's little volume "The Care and Feeding of Children" (1894) went through seventy-five printings and was translated into Spanish, Russian and Chinese. Dr. John M. Keating published "A Cyclopedia of Diseases of Children" in 1890, and Holt wrote the article on diarrheal diseases in infancy, which was the best publication of the period on this subject. He had in his mind, however, a more ambitious project, and for six years he was busily engaged in the preparation of "The Diseases of Infancy and Childhood," which was published in 1896. It became popular almost immediately and was accepted as the standard textbook by students and practitioners alike. The book, written from an extensive clinical and pathologic experience, furnished ample references to the medical literature and contained pathologic descriptions of disease, which increased its value.

Holt was one of the charter members of the American Pediatric Society and was twice its president. He was deeply interested in its proceedings and practically never missed a meeting. His colleagues found him courteous but never effusive; he carried himself with calmness and dignity. When he spoke he was listened to with rapt attention. His subjects were well chosen, and his descriptions were concise and well delivered. At the social gatherings and at the deliberations of the Council where he sat was the head of the table.

He was primarily a clinician and a clinical teacher, though in his later years, in association with Courtney and Fales, he undertook the study of such chemical problems as reliable analyses of human milk and comprehensive studies of the metabolism of calcium and fat. Holt planned the work, interpreted the data and wrote the papers; the actual determinations were made by the others.

Though Holt was a clinician, his outstanding contribution was as an educator. He was a teacher of teachers. He trained physicians, nurses, students and interns and the public in general.

It was largely through his influence with John D. Rockefeller Jr. that the Rockefeller Institute was founded. Holt became a member of the board of directors of the Institute and continued to hold this position throughout the remainder of his life.

As chairman of the Child Health Organization, Holt gave a new impetus to child welfare in the United States.

Immediately after the World War, Holt, among other distinguished American physicians, was appointed to a committee to represent this country at a meeting of the international Red Cross organizations. The committee met at Cannes, France, on April 2, 1919. Dr. Holt became general secretary for this conference; he wrote the report on child welfare and was an influential member of the organization.

Holt's influence in the prevention of infant mortality was felt in many directions. He enlisted the facilities of the Rockefeller Institute in studying the effects of milk contamination among New York's tenement population. He was a member of a committee of physicians who advised the health department of the city on milk regulations. As a member of the board of directors of the famous Henry Street Settlement he gave them a medical point of view, and he taught through his students the lessons learned in the fight against infant mortality, particularly the importance of a pure milk supply.

The book contains many interesting letters to members of his family, which indicate his devotion to them and the depth of his inner feelings. He advised his children to keep their moral standards high, to practice industry and to be self reliant and ambitious.

To his son, Emmett, he wrote: "I wish I could bequeath to you the results of my forty years of experience in medicine, so that you might be able to begin where I shall leave off. But I am afraid it might not prove the blessing that one might imagine, for it is one of the rules of life that it is our own experience which develops us and not that of others who would fain give it to us.

"I still hope that you may begin practice before I retire altogether, and I am sure there are ways in which I might help you a good deal, though I am impressed with the fact that the medicine of the future is to be very different from the medicine of my time."

Speaking further of the future of medicine in his presidential address to the American Pediatric Society in 1923, Holt predicted that laboratory medicine and preventive medicine would come into their own. He could foresee that the paths of the experimenter, the health expert and the practitioner of clinical pediatrics would diverge until they became quite separate, though he thought it important that neither the experimenter nor the health expert should be cut off from clinical pediatrics.

This little volume, "L. Emmett Holt, Pioneer of a Children's Century," records the life story of an illustrious leader who devoted his years to helping place pediatrics on a sound foundation in America and to advocating a system for the preservation of child health.

Children in the Family. By Dr. Florence Powdermaker and Louise Ireland Grimes. Price, $2. Pp. 403, with no illustrations. New York: Farrar & Rinehart, Inc., 1940.

A good child psychiatrist, well informed about the mental growth and development of children, and an observing mother with an objective point of view collaborated in the writing of this book. They discussed the psychologic problems commonly encountered by parents in the rearing of normal children. They combined a scientific and a practical viewpoint in suggesting the logical way to solve each problem.

The book is divided into five parts, which are concerned with infancy, the second year, the age from 2 to 6, the early school years and adolescence. The first half of the book deals with the first four years of life; the second half has to do with the school years, puberty and adolescence.

Technical terms are not used. The material is presented in an interesting way and can easily be understood by the laity. It can be safely recommended to parents.

Wolf Child and Human Child. By Dr. Arnold Gesell. Price, $2.00. Pp. 133, with 6 illustrations. New York: Harper & Brothers, 1941.

This is the fascinating, true and scientific story of Kamala, the wolf girl, who in early infancy was carried away by a female wolf. She lived with wolves until she was 9 years old, when she was captured and taken to an orphanage, where she lived until her death, at 17 years of age.

Dr. Gesell used the carefully kept records of the orphanage as the basis for his study of the mental growth of Kamala. In addition to describing her adaptation to life in the orphanage, he pointed out the effect of hereditary and environmental factors on her development. The case record, with its implications, is of great scientific value for the evaluation of the interrelation of heredity and culture.

In this volume Dr. Gesell has improved on his previous high literary standards, perhaps because the subject allowed him some use of a "scientific imagination."

Strange Malady. By Warren T. Vaughan, M.D. Price, $3.00. Pp. 268, with 23 illustrations. New York: Doubleday, Doran & Company, Inc., 1941.

This excellent book is the second in the series sponsored by the American Association for the Advancement of Science and addressed to the intelligent layman. The problems of allergy are as complicated and confusing as any in medicine, but Dr. Vaughan has discussed them in a most interesting and understanding manner. His chapters on immunology are particularly noteworthy for their clarity of presentation. The 23 well annotated line drawings aid in gaining a clear mental picture of the fundamentals of the subject.

"Strange Malady" is a book which will go far toward educating the general public to a better understanding of the medical enigma of allergy.

Hemorrhagic Diseases: Photo-Electric Study of Blood Coagulability. By Kaare K. Nygaard, M.D. Price, $5.50. Pp. 320, with 59 figures and 56 tables. St. Louis: C. V. Mosby Company, 1941.

This book is divided into three portions. The first part deals with the determination of blood coagulability and the use of the photelegraph, which represents graphically the entire process of coagulation. Part two is concerned with the physiology of blood coagulation and part three with hemorrhagic diseases, of which hemophilia, thrombocytopenic purpura, diseases of the liver and gallbladder and hemorrhagic disease of the newborn are considered in detail. The chapters on vitamin K and hemorrhage due to disorders of the liver and gallbladder contain some interesting information based on the author's research.

Manual of Clinical Chemistry. By Miriam Reiner, M.Sc. Price, $3.00. Pp. 296, with 18 illustrations. New York: Interscience Publishers, Inc., 1941.

The chemical determinations of value to the clinician are given in detail, together with directions for preparing the required reagents. The book is compact, well organized and well printed on a good grade of paper. The subjects covered are the analysis of blood, including quantitative determinations of sulfanilamide and arsenic; the chemical examination of urine, cerebrospinal fluid, feces and gastric contents; testing for poisons, hormones and vitamins, and the determination of renal and hepatic function. The subject index is well prepared, and there is also an author index.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Prof. Dr. J. van Lookeren Campagne, Hofstraat 16, Gröningen, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

---

*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Julius H. Hess, 104 S. Michigan Ave., Chicago.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Cleveland. Time: June 2-6, 1941.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Philadelphia.
Region III. Place: Palmer House, Chicago. Time: May 15-17, 1941.
Region IV. Place: Los Angeles. Time: May 1-3, 1941.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Hot Springs, Va. Time: May 22-24, 1941.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital. Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Vancouver, B. C. Time: June 21, 1941.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.
Place: Del Monte. Time: May 1941.

Florida State Pediatric Society

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.
Place: Chicago. Time: May 1941.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.
Place: Biloxi. Time: May 12, 1941.

Nebraska Pediatric Society

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Marion Y. Keith, 369 N. Elm St., Greensboro.
Secretary: Dr. G. W. Kutscher Jr., 176 Woodfin St., Asheville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. C. P. Jasperson, 509 Nixon Bldg., Corpus Christi.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Fort Worth. Time: May 14, 1941.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. A. L. Newcomb, 1791 W. Howard St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.